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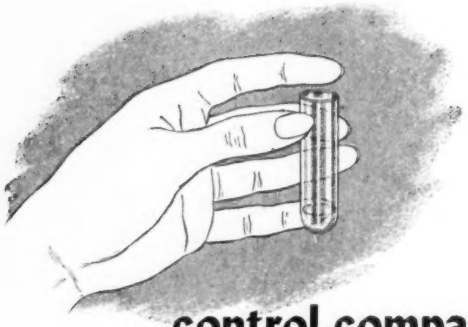

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Sprague, R. G.: Cortisone and ACTH, Am. J. Med. *10*:567, 1951

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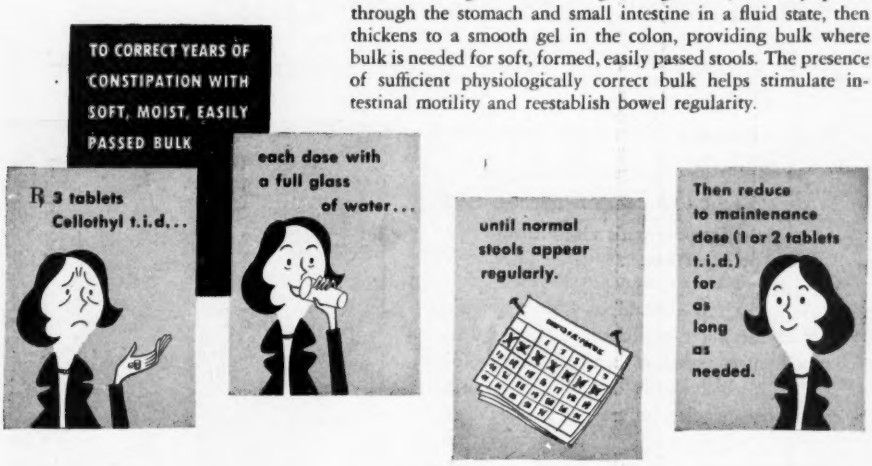
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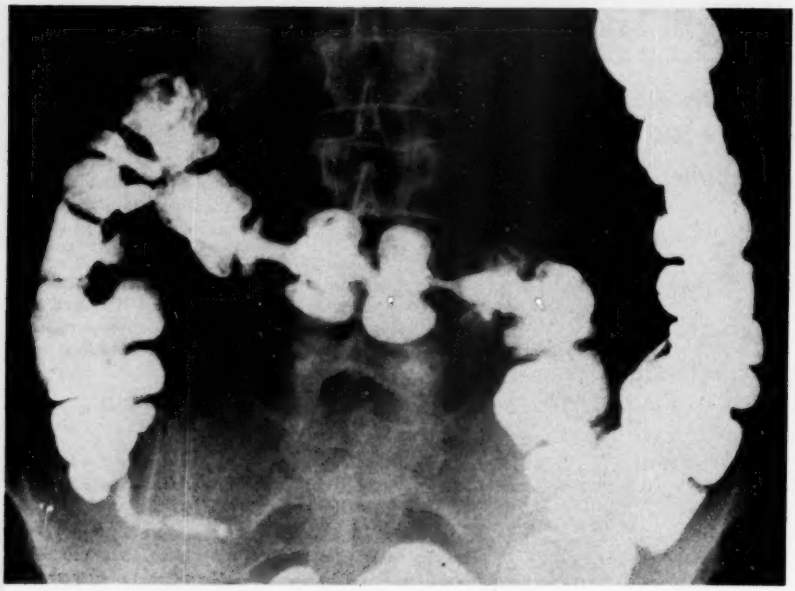

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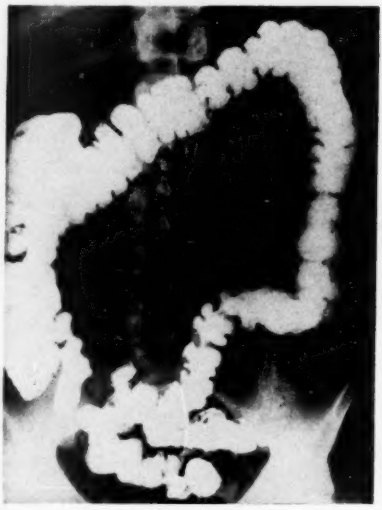

Normally filled colon.

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

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THE A. M. A. ARCHIVES OF INTERNAL MEDICINE is published by the American Medical Association for the advancement of scientific medicine in the United States and for the reporting of research and observation in the domain of internal medicine.

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ARCHIVES OF INTERNAL MEDICINE

VOLUME 89 JANUARY 1952 NUMBER 1

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Editorials

LETTER FROM THE EDITORIAL BOARD

The Editorial Board of the ARCHIVES OF INTERNAL MEDICINE is gratified to announce the addition of three new members to its group and the reelection of one of its veteran members, Dr. Russell Wilder, for another five-year term. Each of the new associate editors has a record of important original scientific investigation in the field of his special interest—Dr. Hugh Butt in gastrointestinal disease, Dr. Louis Leiter in renal disease, and Dr. Bruce Wiseman in hematology.

A little over a year ago the Editorial Board of the ARCHIVES announced its intention of publishing the articles it deemed worthy of acceptance within four months of the time they had cleared the Editorial Board. With extremely few exceptions, this time limit has been met. When the interval was longer, the cause was usually delay in receipt of corrected proof from the authors after the paper had been set in type. It is sincerely hoped that the additions to the Editorial Board will eliminate some of the delay in decisions as to acceptance of articles. This delay has in the past often been unavoidable when all but one or two of the editors have been on vacation or out of the country. With the addition of new associates of high scientific accomplishment, we are confident that careful scrutiny and screening of new material will be maintained, but the period of editorial inspection should seldom exceed one month. The response of both contributors and readers to the efforts to bring important new ideas and techniques to internists with minimum delay has been most heartening. The Editorial Board is deeply grateful and pledges itself to continue these efforts.

PAUL S. RHOADS, M.D.,
Chief Editor.

HUGH R. BUTT, M.D.

Dr. Butt was born Jan. 8, 1910, in Belhaven, N. C., and attended Virginia Polytechnic Institute before entering the University of Virginia from which he received his degree of Doctor of Medicine in 1933. In 1937 he received the degree of Master of Science in Medicine from the University of Minnesota. After interning a year at St. Luke's Hospital, Bethlehem, Pa., he entered the Mayo Foundation, Rochester, Minn., as a Fellow in Medicine in 1934 and was made First Assistant in the Division of Medicine in 1937. He has been a Consulting Physician of the Mayo Clinic and St. Mary's Hospital since 1938, serving as Instructor in Medicine, Mayo Foundation, University of Minnesota, until 1943 and as Assistant Professor from 1943 to 1947. Since 1947 he has held the rank of Associate Professor.

He first gained wide recognition by his work on vitamin K with Dr. Albert Snell and others and has published many papers on other aspects of nutrition (particularly with Dr. Russell M. Wilder) and gastrointestinal disease. His chief interest within the field of internal medicine is still gastroenterology.

LOUIS LEITER, M.D.

Dr. Leiter was born in Falticeni, Rumania, Oct. 24, 1898. After attending McGill University, Montreal, Canada, and the University of Chicago, he entered Rush Medical College, Chicago, receiving his degree of Doctor of Medicine in 1922. He had received his degree of Master of Science in the department of physiology, University of Chicago, in 1919 and won his Doctor of Philosophy degree in pathology at the same university in 1924. His internship and residency years were spent at Cook County Hospital, Chicago, 1921 to 1923, and the Hospital of the Rockefeller Institute for Medical Research, New York, 1924 to 1926. He was Fellow of the National Research Council, 1923-1924.

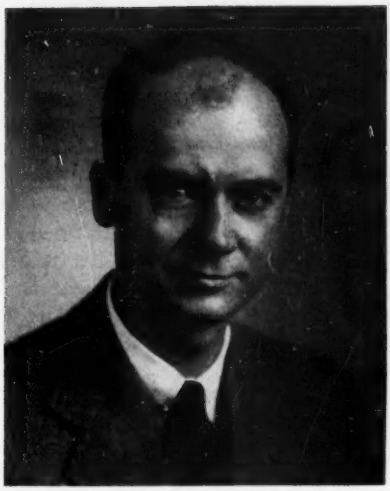
His teaching began at the University of Chicago School of Medicine, where he was Assistant Professor, then Associate Professor, 1926 to 1941, in charge of the section on renal and vascular diseases. He became Clinical Professor of Medicine in 1942. The same year he transferred with the same rank to Columbia University College of Physicians and Surgeons. At present he is full-time Chief of the Medical Division, Montefiore Hospital, New York.

Dr. Leiter's chief research interest has been in the fields of nephritis, hypertension and congestive heart failure. He has carried on many fundamental investigations in nephritis and written the sections on diseases of the kidneys in several medical textbooks, in addition to the articles and monographs reporting his own studies.

BRUCE K. WISEMAN, M.D.

Dr. Wiseman was born in South Bend, Ind., March 1, 1897. After two years at Butler College, Indianapolis, he transferred to Indiana University and received his Doctor of Medicine degree from its School of Medicine in 1928. He was the winner of the Ravdin Gold Medal for highest scholarship during the four years of medicine.

He was a house officer at Indianapolis City Hospital, 1928 to 1930, and then went to New York to become Assistant in the department of bacteriology and pathology at the Rockefeller Institute for Medical Research. It was here that his



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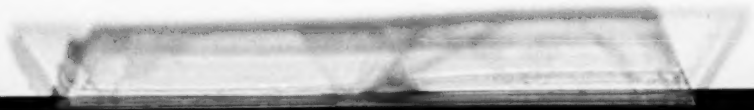


profound interest in the study of lymphocytes began. Many fundamental observations on the morphology and life cycle of these cells which have influenced modern hematologic concepts resulted from these studies. He worked with Dr. F. P. Mallory in the department of pathology, Boston City Hospital, in the summer of 1931 and at the Russell Sage Institute, New York Hospital, in the summer of 1932. He became Assistant Professor of Medicine and Associate Director of Medical Research at Ohio State University in 1931 and was promoted to Associate Professor of Medicine in 1935, and to Professor of Medicine in 1938.

He became Chairman of the Department of Medicine in 1944 and has continued in that position and as Associate Director of Medical Research to the present. He has been Chief of Staff of the Ohio State University Hospital since 1948. He has contributed to the medical literature forty-two articles on various phases of investigative and clinical hematology, among which his fundamental observations on splenic neutropenia are particularly well known.

ENDEMIC INFECTIOUS HEPATITIS IN AN INFANTS' ORPHANAGE

I. Epidemiologic Studies in Student Nurses

RICHARD B. CAPPS, M.D.

ALFRED M. BENNETT, M.D.

CHICAGO

AND

JOSEPH STOKES JR., M.D.

PHILADELPHIA

ALTHOUGH the clinical and pathologic aspects of the infectious (epidemic) type of viral hepatitis are now relatively well understood, the epidemiology of the disease is still not entirely clear. Studies in this field have been seriously handicapped by the lack of a susceptible laboratory animal. Since it has been necessary to employ volunteers, experimental observations have been limited.

It is agreed that the etiological agent of infectious (epidemic) hepatitis is a filtrable virus which can be demonstrated in both the blood and the feces.[1] Not only has the disease been experimentally transmitted by the parenteral injection of infected blood or serum and by the oral ingestion of infected feces but epidemics have been described as presumably due to these mechanisms. Thus, accidental parenteral transmission has been reported as occurring in a variety of ways.[2] Like-

This work was done in part under a contract from the Surgeon General's Office, United States Army, and under the sponsorship of the Commission on Liver Disease, Armed Forces Epidemiological Board. The study was also aided by the Winfield Peck Memorial Fund.

From the Department of Medicine, Northwestern University Medical School, and the Liver Research Laboratory of St. Luke's Hospital (Dr. Capps and Dr. Bennett), and from the Department of Pediatrics, University of Pennsylvania School of Medicine and the Children's Hospital of Philadelphia (Dr. Stokes).

1. (*a*) Voegt, H.: Zur Aetiologie der Hepatitis epidemica, München. med. Wchnschr. **89**:76 (Jan. 23) 1942. (*b*) Cameron, J. D. S.: Infective Hepatitis, Quart. J. Med. **12**:139 (July) 1943. (*c*) MacCallum, F. O., and Bradley, W. H.: Transmission of Infective Hepatitis to Human Volunteers, Lancet **2**:228 (Aug. 12) 1944. (*d*) Havens, W. P., Jr.; Ward, R.; Drill, V. A., and Paul, J. R.: Experimental Production of Hepatitis by Feeding Icterogenic Materials, Proc. Soc. Exper. Biol. & Med. **57**:206 (Nov.) 1944. (*e*) Findlay, G. M.; Martin, N. H., and Mitchell, J. B.: Hepatitis After Yellow Fever Inoculations: Relation to Infective Hepatitis, Lancet **2**:301 (Sept. 2); 340 (Sept. 9); 365 (Sept. 16) 1944. (*f*) Neefe, J. R.; Stokes, J., Jr., and Reinhold, J. G.: Oral Administration to Volunteers of Feces from Patients with Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis, Am. J. M. Sc. **210**:29 (July) 1945.

2. (*a*) Havens, W. P., Jr.: Infectious Hepatitis, Medicine **27**:279 (Sept.) 1948. (*b*) Neefe, J. R.: Recent Advances in Knowledge of "Virus Hepatitis," M. Clin. North America **30**:1407 (Nov.) 1946. (*c*) Capps, R. B.; Sborov, V., and Scheifley, C. H.: A Syringe-Transmitted Epidemic of Infectious Hepatitis, J. A. M. A. **136**:819 (March 20) 1948.

wise, there are several reports of epidemics due to contaminated water,[3] milk,[4] and food.[5]

On the other hand, the possibility of transmission by the respiratory route is still not clearly settled. There is suggestive experimental evidence of virus in nasal washings [6] which has not been confirmed by subsequent work.[7] Attempts to infect volunteers through the nasal mucosa [6b] are open to the objection that the infected material may be swallowed and so actually enter through the gastrointestinal tract. In addition, Gauld has interpreted certain epidemiologic data as indicating respiratory transmission.[3b] The problem is important because some type of person-to-person contact appears to be the commonest form of spread,[2a] and the respiratory as well as the gastrointestinal route might easily be involved.

Finally, there is evidence that virus may be present in the urine.[8] At present, however, this appears improbable in view of the failure of subsequent attempts to verify these findings,[7] as well as Findlay's more recent conclusions [9] casting doubt on his original observations.

In contrast to the relatively clear-cut situation regarding transmission, few data are available concerning the mechanisms responsible for keeping the infection or epidemic alive. It is frequently difficult or impossible to determine the source of infection in individual cases. Since no animal host has yet been found, the possibility of prolonged periods of infectiousness or of the existence of many unrecognized acute cases must be entertained. So far, a fecal carrier state has not been demonstrated, although one inconclusive experiment suggests persistence of the virus for five months after onset.[10] In other reports, limited in number, the virus has been found in the feces during only the first two weeks of illness.[11] On the other hand,

3. (*a*) Neefe, J. R., and Stokes, J., Jr.: An Epidemic of Infectious Hepatitis Apparently Due to a Water Borne Agent, J. A. M. A. **128**:1063 (Aug. 11) 1945. (*b*) Gauld, R. L.: Epidemiological Field Studies of Infectious Hepatitis in Mediterranean Theatre of Operations, Am. J. Hyg. **43**:248 (May) 1946. (*c*) Fraser, R.: A Study of Epidemic Catarrhal Jaundice, Canad. Pub. Health J. **22**:396 (Aug.) 1931.

4. Murphy, W. J.; Petrie, L. M., and Work, S. D., Jr.: Outbreak of Infectious Hepatitis, Apparently Milk-Borne, Am. J. Pub. Health **36**:169 (Feb.) 1946.

5. Read, M. R.; Bancroft, H.; Doull, J. A., and Parker, R. F.: Infectious Hepatitis: Presumedly Food-Borne Outbreak, Am. J. Pub. Health **36**:367 (April) 1946.

6. (*a*) MacCallum and Bradley.[1c] (*b*) Findlay, G. M., and Martin, N. H.: Jaundice Following Yellow Fever Immunization: Transmission by Intranasal Instillation, Lancet **1**:678 (May 29) 1943.

7. (*a*) Neefe and Stokes.[3a] (*b*) Havens, W. P., Jr.: The Period of Infectivity of Patients with Experimentally Induced Infectious Hepatitis, J. Exper. Med. **83**:251 (March) 1946.

8. (*a*) Footnote 1*a* and *c*. (*b*) Findlay, G. M., and Willcox, R. R.: Transmission of Infective Hepatitis by Feces and Urine, Lancet **1**:212 (Feb. 17) 1945.

9. Findlay, G. M.: Infective Hepatitis in West Africa, Month. Bull. Min. Health & Pub. Health Lab. Serv. **7**:2 (Jan.) 1948.

10. Neefe, J. R.; Stokes, J., Jr.; Garber, R. S., and Gellis, S. S.: Studies on Relationship of Hepatitis Virus to Persistent Symptoms, Disability and Hepatic Disturbance Following Acute Infectious Hepatitis, J. Clin. Invest. **26**:329 (March) 1947.

11. Neefe and others.[1f] Havens.[7b] Findlay and Willcox.[8b] Neefe, J. R.; Gellis, S. S., and Stokes, J., Jr.: Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis: Studies in Volunteers Bearing on Immunological and Other Characteristics of the Etiological Agents, Am. J. Med. **1**:3 (July) 1946.

the existence of nonicteric forms of acute hepatitis is well established.[12] As previously pointed out by one of us,[2c] they may represent 90% of the cases in a given epidemic, although the figure is naturally quite variable. However, the exact epidemiologic role played by this group is not known.

In July, 1949, at the invitation of Dr. Louis Sauer, an investigation was undertaken of an epidemic of hepatitis in an orphanage for infants and small children. The results have served to clarify some of the above problems. The outbreak was remarkable because only student nurses appeared to be involved and because it had been in progress since 1942. A preliminary analysis of the situation suggested that the children were serving as an unrecognized endemic focus. The validity of this hypothesis was established by a study of the subsequent course of the epidemic in both nurses and children. Preliminary reports of this investigation have been presented before the American Society of Clinical Investigation [13] and the American Clinical and Climatological Association.[14] The present paper is a final report covering in detail the nature of the epidemic and the observations relative to the nurses. Epidemiologic studies in the children [15] and a description of the clinical picture in this age group [16] will be the subjects of later communications.

METHODS

Data regarding the course of the epidemic prior to August, 1949, were obtained from the orphanage records. During this period only persons with a history of clinical jaundice were accepted as having had viral hepatitis. Beginning in August, 1949, all clinical and laboratory observations were made by us. The latter were carried out in the Liver Research Laboratory of St. Luke's Hospital. An initial survey of all nurses for liver disease was made in August and September. Then, commencing with the September class, new student nurses were routinely surveyed, in a similar fashion, on admission in order to obtain an individual base line in case of subsequent illness. In October, serial laboratory studies were commenced on the infants and children.

The following laboratory procedures were performed on blood samples, both Evelyn and Coleman electrophotometers being used for photometric determinations. The serum bilirubin was determined by the Ducci and Watson [17] modification of the method of Malloy and Evelyn.[18]

12. (*a*) Neefe, J. R.; Stokes, J., Jr.; Reinhold, J. G., and Lukens, F. D. W.: Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers, J. Clin. Invest. **23**:836 (Sept.) 1944. (*b*) Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theater Including Acute Hepatitis Without Jaundice, J. A. M. A. **128**:997 (Aug. 4) 1945.

13. Capps, R. B.; Bennett, A. M., and Stokes, J., Jr.: A Prolonged Outbreak of Infectious Hepatitis in Nurses Due to a Group of Small Children Serving as a Reservoir of the Virus, J. Clin. Invest. **29**:802 (June) 1950.

14. Capps, R. B., and Bennett, A. M.: Clinical and Epidemiological Investigations Concerning Viral Hepatitis in Infants and Small Children, Proc. Am. Clin. & Climatol. A. **62**:98, 1950.

15. Bennett, A. M.; Capps, R. B.; Drake, M. E.; Ettinger, R. H.; Mills, E. H., and Stokes, J., Jr.: Endemic Infectious Hepatitis in an Infants' Orphanage: II. Epidemiologic Studies in Infants and Small Children, to be published.

16. Capps, R. B.; Bennett, A. M.; Mills, E. H.; Ettinger, R. H.; Drake, M. E., and Stokes, J., Jr.: The Clinical Picture and Diagnosis of Infectious Hepatitis in Infants and Small Children with Special Reference to the Nonicteric Form, to be published.

17. Ducci, H., and Watson, C. J.: The Quantitative Determination of the Serum Bilirubin with Special Reference to the Prompt-Reacting and the Chloroform-Soluble Types, J. Lab. & Clin. Med. **30**:293 (April) 1945.

18. Malloy, H. T., and Evelyn, K. A.: Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

The serum alkaline phosphatase was measured by the Bodansky method [19] and the phosphorus according to Gomori's procedure.[20] The sulfobromophthalein (bromsulphalein®) sodium retention was measured at 45 and 60 minutes after a dose of 5 mg. per kilogram of body weight, using the method of Gaebler.[21] Standard methods were employed for the following tests: thymol turbidity and flocculation,[22] cephalin-cholesterol flocculation,[23] scarlet red flocculation,[24] and cholesterol esters level.[25] The Reinhold and Neefe [26] curve with a normal value of 2.0 units was employed for the thymol turbidity determination. Cholinesterase was determined according to Michel [27] and the ammonium sulfate turbidity according to de la Huerga and Popper.[28] Quantitative 24-hour coproporphyrin and urobilinogen [29] excretions were measured in the urine, and occasionally the two-hour urobilinogen method [30] was employed. Routinely, the urine was tested for bilirubin by the methylene blue [12] and the barium-strip test.[31]

Similar methods were used for studying the infants. The smaller quantity of available blood made certain modifications necessary. These will be described in a later communication.[16]

THE ORPHANAGE AND PERSONNEL

Patients.—The orphanage is a five-story building with wards for patients and living quarters for personnel arranged as shown in Table 1. The infants and children, averaging 180 in number, are all less than 3 years old. Newly admitted

19. Bodansky, A.: Phosphatase Studies: Determination of Serum Phosphatase; Factors Influencing the Accuracy of the Determination, J. Biol. Chem. **101**:93 (June) 1933.

20. Gomori, G.: A Modification of the Colorimetric Phosphorus Determination for Use with the Photoelectric Colorimeter, J. Lab. & Clin. Med. **27**:955 (April) 1942.

21. Gaebler, O. H.: Determination of Bromsulphalein in Normal, Turbid, Hemolyzed or Icteric Serums, Am. J. Clin. Path. **15**:452 (Oct.) 1945.

22. Maclagan, N. F.: The Thymol Turbidity Test as an Indicator of Liver Dysfunction, Brit. J. Exper. Path. **25**:234 (Dec.) 1944. Shank, R. E., and Hoagland, C. L.: A Modified Method for the Quantitative Determination of the Thymol Turbidity Reaction of Serum, J. Biol. Chem. **162**:133 (Jan.) 1946.

23. Hanger, F. M.: Serological Differentiation of Obstructive and Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Invest. **18**:261 (May) 1939.

24. Ducci, H.: The Colloidal Red Test for the Study of Hepatic Dysfunction, J. Lab. & Clin. Med. **32**:1273 (Oct.) 1947.

25. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, J. Biol. Chem. **106**:745 (Sept.) 1934. Clarke, D. H., and Marney, A. F.: The Determination of the Free and Total Cholesterol of Plasma with the Photoelectric Colorimeter, J. Lab. & Clin. Med. **30**:615 (July) 1945.

26. Reinhold, J. G., and Neefe, J. R.: Personal communication to the authors.

27. Michel, N. O.: An Electrometric Method for the Determination of Red Blood Cell and Plasma Cholinesterase Activity, J. Lab. & Clin. Med. **34**:1564 (Nov.) 1949.

28. de la Huerga, J., and Popper, H.: Estimation of Serum Gamma Globulin Concentration by Turbidimetry, J. Lab. & Clin. Med. **35**:459 (March) 1950.

29. Schwartz, S.; Hawkinson, V.; Cohen, S., and Watson, C. J.: A Micromethod for the Quantitative Determination of the Urinary Coproporphyrin Isomers (I and III), J. Biol. Chem. **168**:133 (April) 1947. Schwartz, S.; Sborov, V., and Watson, C. J.: Studies of Urobilinogen: The Quantitative Determination of Urobilinogen by Means of the Evelyn Photoelectric Colorimeter, Am. J. Clin. Path. **14**:598 (Dec.) 1944.

30. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: A Simple Method for the Quantitative Recording of the Ehrlich Reaction as Carried out with Urine and Feces, Am. J. Clin. Path. **14**:605 (Dec.) 1944. Watson, C. J., and Hawkinson, V.: Studies of Urobilinogen: VI. Further Experience with the Simple Quantitative Ehrlich Reaction: Corrected Calibration of the Evelyn Colorimeter with a Pontacyl Dye Mixture in Terms of Urobilinogen, ibid. **17**:108 (Feb.) 1947.

31. Hawkinson, V.; Watson, C. J., and Turner, R. H.: A Modification of Harrison's Test for Bilirubin in the Urine Especially Suited for Mass and Serial Usage, J. A. M. A. **129**:514 (Oct. 13) 1945.

children, after passing through the receiving department, are sent to either the fourth or the fifth floor according to age. Infants born in the maternity ward are put in the newborn nursery on the same floor until taken home or transferred to the fifth-floor nursery. Both the fourth and the fifth floors are divided into several wards containing 10 to 25 beds each. These groups are relatively isolated from each other, but within each group the children play together and are in close contact. Although the average stay in the orphanage is four months, it is quite variable and frequently is one to two years.

The maternity patients include about 15 unmarried expectant mothers who live in the institution two to four months prior to delivery and 25 to 30 other maternity patients per month who are admitted for delivery only. The former group, especially, has served as an ideal control for the student nurses, since they represent the same age group, live in a separate wing on the same floor, drink the same water, and eat the same food. All obstetrical patients are examined routinely six weeks

TABLE 1.—*Average Census and Length of Stay of Patients and Resident Personnel*

Floor	Purpose	Average Census	Age	Average Stay
Ground	Receiving ward	42	0-1 yr.	3 wk.
		3	1-3 yr.	3 wk.
1st	Maternity ward	12	Adults	8 days
	Newborn nursery	16	Newborn	12 days
	Residents' quarters	3	Adults	1 yr.
2d	Sisters' quarters	14	Adults	4 yr.
	Student nurse quarters	25	Adults	1 yr.
3d	Expectant mothers	15	Adults	3 mo.
	Student nurse quarters	25	Adults	1 yr.
4th	Children's wards	45	1-3 yr.	4 mo.
5th	Children's wards	70	0-1 yr.	4 mo.

post partum and subsequently visit or correspond with the nursing sisters, so that any unusual illness is reported.

Personnel.—In addition to the resident personnel shown in Table 1, 10 maids and cooks live in quarters scattered throughout the building. The student nurses have averaged 50 in number since 1946 and receive a one-year course. Previously, there were only about 25 and an equal number of affiliates who changed every three months. Most of the new girls are admitted to training in March, June, and September, although there is no set rule. Each one is rotated throughout all wards in the hospital. Nonresident personnel include about 20 "graduate" nurses, mostly alumnae, and sundry cooks, maids, and other help, and many volunteer workers.

Food and Facilities.—The food, which is provided from a central kitchen, and the water supply are common to all personnel and patients. The main water pipes run vertically, so that contamination from this source should involve vertical sections of the building rather than individual floors. A test for back siphonage from toilets was made with fluorescein and gave essentially negative results. Laundry equipment and supervision are excellent and provide adequate sterilization.

Laboratory facilities are limited. Blood examinations are made monthly on all children, and other routine procedures are done as necessary. Prior to August,

1949, capillary puncture was performed with a needle stuck in a cork and kept in alcohol, which did not provide adequate sterilization. On the other hand, proper aseptic venepuncture technique was employed.

Nursing Technique.—Finally and most important, nursing technique was seriously deficient. Since the orphanage was basically a well-baby institution and not a hospital, the possibility of obscure contagion was not seriously considered. Furthermore, the number of experienced nursing personnel was limited. Reasonable asepsis in nursing procedures was attained only with small infants under approximately 6 months of age with whom individual isolation methods were employed. In the case of the fifth floor and the receiving ward, the care of the children of the older, nonisolated groups was favorably influenced by the presence of small infants on the same floor and, although poor, was distinctly better than in similar groups elsewhere.

On the other hand, on the fourth floor aseptic technique was not seriously attempted. The children played with one another; nurses did not wash their hands

TABLE 2.—*Incidence of Hepatitis in Children's Orphanage in Eight-Year Period, 1942 Through 1949*

	Approximate No.	Hepatitis	%
Student nurses	380	72	19
Graduate nurses	100	1	1
Residents and clerks	64	1	1.6
Other resident personnel	30	0	..
Maternity patients			
Stay 2-4 mo	480	0	..
Delivery only	2,400	1	0.04
Infants, 0-3 yr. of age	6,400	?	..

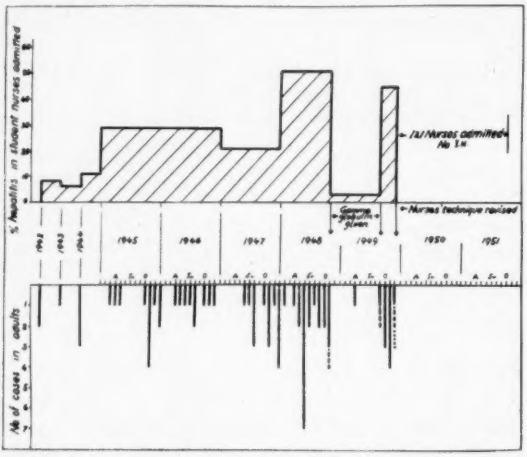
between handling patients, and gowns were changed infrequently. Adequate washbowls with foot or arm controls were not available as on other floors. In addition, the children's toilets were cleaned by hand with washrags by the student nurses. There were no such toilets on the fifth floor and only a few in the receiving ward, which, however, were cleaned in a similar manner. Finally, on both fourth and fifth floors each nurse carried her own thermometer. Temperatures were taken by axilla or rectum. After use, the thermometer was wiped with a piece of gauze moistened with alcohol and replaced in its case. Inquiry revealed that the student often practiced taking her own temperature with the same thermometer when off duty.

GENERAL DESCRIPTION OF THE EPIDEMIC

During the eight-year period from 1942 through 1949, 75 definite cases of acute infectious hepatitis were recognized in adults. The almost exclusive involvement of student nurses is shown in Table 2. Only three cases occurred in other groups. The first case was that of a resident physician in the obstetrical service who became jaundiced in November, 1948. His only known contact was a possibly contagious student nurse on the floor who was convalescing from acute hepatitis. The second case was that of a nursing sister who became ill in September, 1949, three weeks after being transferred to the institution. In the third case, that of an obstetrical patient, jaundice developed 14 days after admission and delivery. A blood trans-

fusion was given at the time of delivery. Since 14 days is less than the usually accepted minimum incubation period, it is probable that she contracted her disease elsewhere. On the other hand, if she did contract it at the hospital, then the blood was a potential source of infection. In either event there is a serious question whether this case is a part of the epidemic.

It must be pointed out that there were probably many more cases than are recorded here during the period prior to August, 1949. Typical histories were frequently obtained from student nurses, but jaundice could not be verified, and laboratory evidence was lacking. This is confirmed by the fact that 4 of the 12 patients, or 33%, personally observed in the fall of 1949 were nonicteric. These persons not only presented the characteristic clinical picture of acute nonicteric hepatitis [12b] but in all instances had confirmatory laboratory findings.


% hepatitis in student nurses admitted
No of cases in adults
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
A
O
N
D
J
F
M
A
M
J
J
A
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this 10-month period, and this patient received the gamma globulin too late for it to be effective. In December, 1949, the epidemic was terminated, as will be subsequently described.

PRELIMINARY ANALYSIS OF DATA

In July, 1949, when this investigation was undertaken, only such data as could be obtained from the orphanage records were available. Fortunately, analysis of this material produced a working explanation of the epidemic. This made it possible to plan a study devised specifically to establish the validity of the hypothesis. In the following data the 12 additional cases which occurred after July, 1949, have been included in order to avoid subsequent repetition. This has not, however, materially altered the original conclusions.

TABLE 3.—*Incidence of Short Incubation Periods in Adults, Showing Elapsed Time from Admission to Onset of Hepatitis*

Days	No. of Cases
14-19	2
20-29	3
30-39	3
40-49	4
50-59	7
60-69	5
70-79	7
80+	44

TABLE 4.—*Elapsed Time Between Admission Blood Studies and Onset of Hepatitis in Adults*

Days	No. of Cases
0- 15	3
16- 42	6
43- 59	2
60- 89	3
90-119	2
120+	5
No blood studies	51
Unknown	3

Type of Virus.—This was readily ascertained by examining incubation periods and the possibility of parenteral transmission. Analysis of the elapsed time between admission to the institution and onset of jaundice is shown in Table 3. In 19 cases the longest possible incubation period was less than 60 days, which is incompatible with the usually accepted figure for homologous serum hepatitis.

The possibility of parenteral transmission was essentially eliminated by the data shown in Table 4. Blood cell counts and serologic tests made on admission provided the only available mechanism for parenteral transfer of the virus. In 51 instances these tests were not performed, and in 11 of the remaining cases the incubation period was too short for homologous serum hepatitis. In addition, the maternity patients failed to have hepatitis in spite of routine admission blood examinations.

Thus, the demonstration of short incubation periods and, especially, the elimination of the possibility of parenteral transmission made it apparent that we were

dealing with the infectious (epidemic) type of viral hepatitis. This conclusion was further supported by the effectiveness of gamma globulin administration in preventing the appearance of new cases.[32]

Transmission.—The above data also indicated that transmission was occurring either by the fecal-oral or by the respiratory route. Food and water were clearly eliminated because of the absence of disease among the maternity patients, as well as among the other resident personnel. In addition, water contamination could not explain the concentration of cases on a single floor, as will be subsequently described. It, therefore, followed that some type of person-to-person contact was responsible for the spread of the virus.

Source of Infection.—The possibility of direct spread between adults was first considered. This could not be satisfactorily investigated because of the poor records of illness and the unknown factor of unrecognized cases. Nurses with the contagious acute disease were not isolated and certainly provided a potential source of infection, particularly for their roommates, but also for others. No epidemiologic evidence of adult carriers could be obtained, although three instances of chronic active hepatitis were discovered on the initial survey.

TABLE 5.—*Working Assignments of Seventy-Three Nurses and One Resident During Exposure Period, Sixteen to Forty-Two Days, Before Onset of Hepatitis* *

Floor	No. of Cases	% of 74	Average Nurse Census
Fourth	56	75	13
Fifth	25	34	21
Receiving	7	10	11
Others	5	7	5

* Many worked on more than one floor.

The possibility of an extraneous endemic focus was suggested by a rumor among the nurses that working on the fourth floor was dangerous and also by the single case occurring during the period of gamma globulin administration. Consequently, an analysis was made of the working assignments of all 74 persons who had hepatitis during the period in which their exposure presumably occurred—16 to 42 days before the onset of illness (Table 5). Many, of course, worked on more than one floor during this period. Seventy-five per cent of the cases developed after fourth-floor exposure, although the average number of girls assigned to this floor at any one time was only 13, or 26% of the total student body. For statistical purposes the situation is simplified by considering only those patients who contracted the disease after exposure on a single floor. A comparison of this group with the expected number of patients if random distribution had prevailed is depicted in Figure 2. The latter data were computed from the average floor census of student nurses, which represents the random chance of exposure on any particular floor. Application of the chi-square rule shows that the difference between actual and expected number of cases is highly significant. Obviously, there was a causal relationship between working on the fourth floor and the development of hepatitis.

32. Stokes, J., Jr.; Blanchard, M.; Neefe, J. R.; Gellis, S. S., and Wade, G. R.: Methods of Protection Against Homologous Serum Hepatitis: I. Studies on the Protective Value of Gamma Globulin in Homologous Serum Hepatitis Virus, J. A. M. A. **138**:336 (Oct. 2) 1948.

The most plausible explanation for this situation appeared to be that the children, particularly on the fourth floor, were infected with the virus. This was consistent with the known deficiency in fourth-floor nursing technique, as well as the frequent handling required in caring for children of this age and the usual presence of fecal contamination.

Plan of Study.—In view of these deductions, it was obviously necessary to obtain convincing evidence of either the presence or the absence of infection in the children. This was of practical importance because extensive nonicteric hepatitis in infants had not been previously described. Establishing the diagnosis of nonicteric hepatitis presents serious difficulties even in adults.

Since the administration of gamma globulin had been discontinued prior to the entry of the September, 1949, class of student nurses, an opportunity was provided to study both the nurses and the children in their customary environment. The observations on these two groups will be described separately.

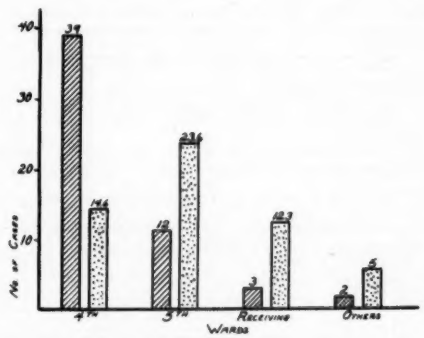

Fig. 2.—Incidence of hepatitis by wards: relation of working assignments to development of hepatitis. Comparison of actual (hatched columns) and expected (dotted columns) distribution of cases among 55 nurses and 1 resident with the disease who were exposed on only one floor for the 16- to 42-day period preceding onset.

STUDIES CONCERNING THE NURSES AFTER SEPT. 1, 1949

A group of 20 new student nurses was admitted to training in September and the first part of October, 1949, and was carefully observed for evidence of liver disease. No changes in institutional routine were made, except for the introduction of an individually sterilized lancet technique for capillary puncture. During the first week of December nursing technique was revised. In January, 1950, and in subsequent months new students were again admitted. No gamma globulin was given, and they were observed as were previous groups.

The revision in nursing technique consisted of indoctrination in the principles of asepsis as concerned in the handling of potentially contagious material. Primarily, this was a matter of frequent and proper hand washing and avoidance of mouth contact with the hands. Adequate washing facilities were installed; thermometers were placed in the wards for patients, and sufficient clean gowns were made available. Face masks were not employed at any time, nor were isolation procedures

extended to the care of children of older age groups. This type of technique was enforced throughout the institution, although it had previously been practiced to a greater or less extent on all floors except the fourth.

The results of this study are shown roughly in Figure 1 and in detail in Figures 3 and 4. As indicated in Figure 3, nine of the first group of student nurses acquired

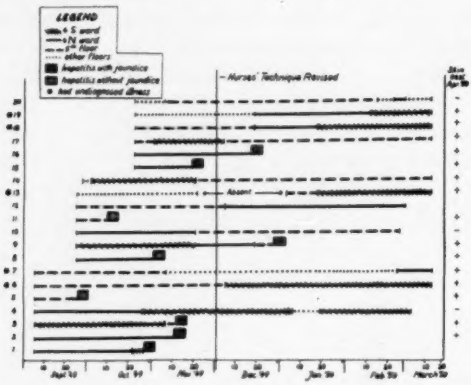

Fig. 3.—Hepatitis in 20 new students admitted in fall of 1949. Working assignments and reactions to skin test in April, 1950, are indicated. Note relation to fourth-floor exposure.

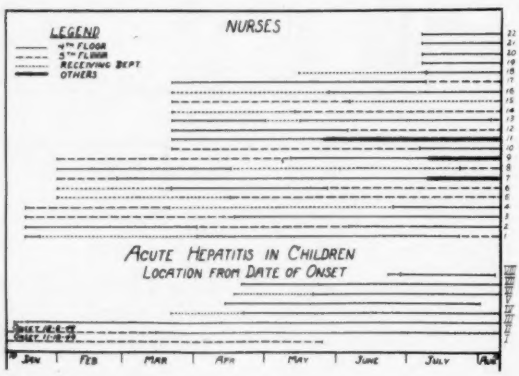

Fig. 4.—Working assignments of student nurses (Jan. 10 to Aug. 10, 1950) with reference to children with hepatitis after change in nursing technique. Nineteen other student nurses were not exposed. Note absence of hepatitis in nurses.

acute infectious hepatitis. Each horizontal line represents a nurse and indicates the floor assignments. Of 11 new student nurses exposed on the fourth floor prior to the change in technique 7 had hepatitis, whereas of 10 exposed on the fifth floor only 2 acquired the disease. It will be noted that among the girls who remained well seven were exposed on the fourth floor only after the change in technique. It is of interest that five patients (Cases 6, 7, 13, 18, and 19) had positive skin

test reactions with a previously described specific material[33] in April, 1950, as indicated in the right-hand column. These girls all had acute illnesses consistent with the clinical picture of acute hepatitis, but confirmatory laboratory evidence could not be obtained. Their condition may represent true subclinical disease.

During the fall of 1949 there were three additional cases of hepatitis in other groups. Those of the maternity patient and the nursing sister have been mentioned previously. The third case, which occurred in December, was that of a student nurse who had received gamma globulin 10 months before. Both the nurse and the sister were exposed on the fourth floor.

As indicated in Figures 1 and 3 there was a striking cessation of the epidemic following the change in the technique within the expected lag period of one month. Infection undoubtedly occurred in the last three cases prior to the change. A total of 121 student nurses have now been admitted to training over a 22-month period, and yet there has not been a single case of hepatitis in this or any other adult group in the institution.

During this time there has been no significant change in institutional routine, except that in nursing technique. Although an attempt was made in January, 1950, to isolate all children with hepatitis in a special ward, this proved to be unsuccessful, and cases have continued to develop up to the present among the children in the open wards. Evidence that student nurses continued to be exposed to infected children is presented in Figure 4. Each horizontal line represents a case of hepatitis in a child or a normal student nurse, with their respective floor assignments. One of these children (Child II) was found to have virus in her feces in March, 1951, as will be subsequently described. It is evident that 22 of the 41 new student nurses admitted during the seven-month period were exposed to infected children. In addition, three of these students worked in the hepatitis isolation ward during this time.

OBSERVATIONS ON INFANTS AND CHILDREN

The primary purpose of the observations on infants and children was to discover whether evidence could be obtained of hepatitis in the children. Beginning in September, 1949, serial clinical and laboratory observations were made on as many infants and children as possible, but with particular emphasis on those on the fourth floor. Control studies were instituted on normal infants, as well as on infants with various types of acute infections in other institutions. The results will be described in detail in subsequent reports,[34] and only the pertinent findings will be presented here.

Clinical and Laboratory Findings.—Twenty-six children were encountered up to July, 1950, with abnormal findings which were sufficiently marked and sufficiently persistent to justify the diagnosis of hepatitis. Many other suspicious cases

33. Henle, G.; Drake, M. E.; Henle, W., and Stokes, J., Jr.: Skin Test for Infectious Hepatitis, Proc. Soc. Exper. Biol. & Med. **73**:603 (April) 1950. Henle, W.; Harris, S.; Henle, G.; Harris, T. N.; Drake, M. E.; Mangold, R., and Stokes, J., Jr.: Studies on the Agent of Infectious Hepatitis: I. Propagation of the Agent in Tissue Culture and in the Embryonated Hen's Egg, J. Exper. Med. **92**:271 (Sept.) 1950. Drake, M. E.; Kitts, A. W.; Blanchard, M. C.; Farquhar, J. A.; Stokes, J., Jr., and Henle, W.: Studies on the Agent of Infectious Hepatitis: II. The Disease Produced in Human Volunteers by the Agent Cultivated in Tissue Culture or Embryonated Hen's Eggs, ibid. **92**:283 (Sept.) 1950.

34. Bennett and others.[15] Capps and others.[16]

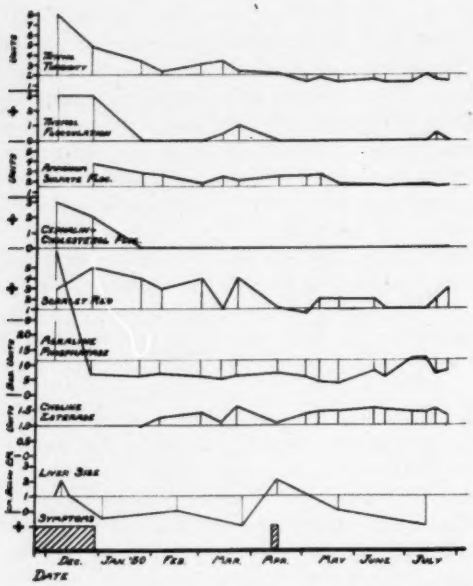

Fig. 5.—Course of acute infectious hepatitis in T. V. H., aged 21 months. Horizontal lines indicate normal values. *C. M.* is costal margin. *Bod. units* means Bodansky units.

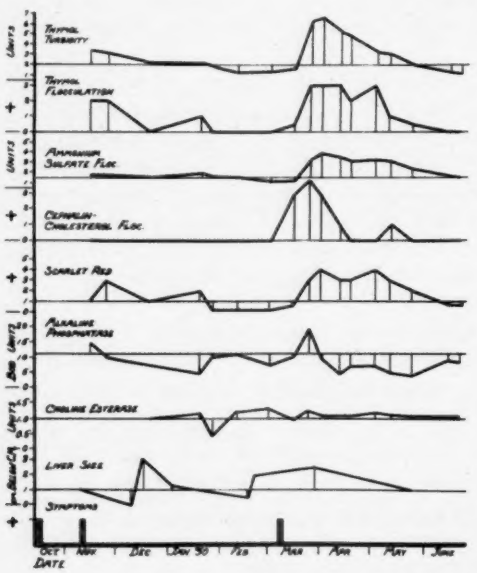

Fig. 6.—Course of infectious hepatitis, probably chronic, in L. K., aged 11 months. Horizontal lines indicate normal values. *C. M.* is costal margin. *Bod. units* means Bodansky units.

were observed. In only one case was hyperbilirubinemia present, but the pattern of this child's findings closely paralleled that of the other patients, with the exception of bilirubinemia. Among the commoner symptoms were loose stools, lassitude, anorexia, and failure to gain weight. A low-grade fever was often present at the onset. The liver usually became enlarged and returned to normal coincident with clinical convalescence.

In Figures 5 and 6 are depicted serial findings in two typical nonicteric cases. The persistence of abnormal reactions will be noted, especially in Figure 6. The

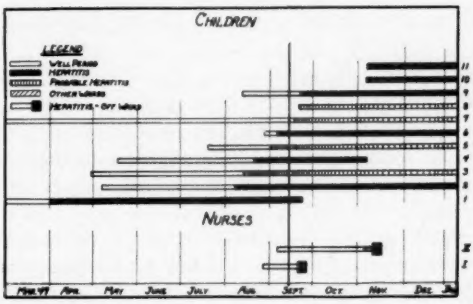

Fig. 7.—Outbreak of hepatitis in a single ward (Ward 4*S*). Mass testing began Sept. 15, 1949. Squares indicate when nurses became ill and left ward. Nineteen other children in the group remained well.

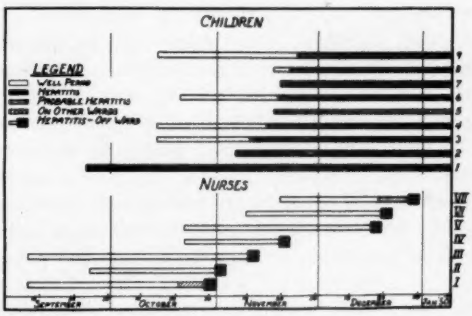

Fig. 8.—Outbreak of hepatitis in a single ward (Ward 4*N*) following introduction of a contagious child (eight other children remained well). Squares indicate when nurses became ill and left ward.

first infant, T. V. H., had loose stools on Nov. 25. On Dec. 1, there was anorexia, vomiting, abdominal distention, lethargy, and slight fever lasting for one week. On April 14, there was a transitory recurrence of fever.

The second infant, L. K., had loose stools and low-grade fever beginning Oct. 13 and lasting four days. There was a transitory recurrence of fever on Nov. 15. Again on March 15, there were loose stools and fever for several days.

Epidemiologic Data.—Epidemiologic observations strongly confirmed the existence of infectious hepatitis in the children.[15] The spread of the disease in two of the fourth-floor wards is shown in Figures 7 and 8. Horizontal bars represent

individual cases. The date of onset is taken as that of onset of symptoms, provided this did not precede the first positive result on liver-function tests by more than 10 days. The serial rather than explosive spread of the disease among the children, as well as the nurses, is obvious. The fact that both nurses and children became ill simultaneously in the same ward in a similar manner is rather convincing evidence that the children were infected with the same virus as the nurses.

Skin tests with a previously described antigen [33] substantiated our clinical diagnosis and indicated that infectious hepatitis was prevalent among the children on the fifth floor and in the receiving ward, as well as on the fourth floor. Acute cases were also recognized clinically on all three floors and occasionally at the time of admission.

Volunteer Experiments.—Conclusive proof that the children were infected with the virus and that our diagnostic criteria were valid was obtained from experiments with volunteers. Filtered fecal material from each of two children with clinical evidence of infectious hepatitis fed to adult volunteers produced typical infectious hepatitis with jaundice. This investigation will subsequently be reported on in detail.[35]

OBSERVATIONS CONCERNING GAMMA GLOBULIN

Seventy-one student nurses received a single dose of gamma globulin (0.06 cc. per pound [0.12 cc. per kilogram] of body weight) during the 10-month period beginning Nov. 4, 1948. Thirty-one were "old" students when they received their injection in November, 1948, having been in the institution for three months or more. Although none of this group acquired clinical hepatitis, they must be disregarded because they were members of nursing classes with a high incidence of diagnosed disease and, therefore, were potentially immune either because of unrecognized infection while in training or because of a prior infection. The remaining 40 were "new" student nurses admitted between Oct. 20, 1948, and June 8, 1949. Thirty-six of these essentially completed their one-year period of training. The other four withdrew after less than three weeks and so need not be considered here, although they were not reported as sick. Six were graduated the last week of October, 1949, whereas 30 remained in training until some time in 1950. In 23 of these 36 student nurses the gamma globulin was given within one month of admission, whereas in the other 13 it was given between one and three months after admission.

Only 2 of the 36 exhibited recognized hepatitis. One nurse who acquired hepatitis in April, 1949, (Fig. 1) received the gamma globulin two days before the appearance of jaundice, obviously too late to be effective.[32] The other became jaundiced in December, 1949, approximately nine months after receiving gamma globulin. It is of interest that this patient did not work on the fourth floor until two months before becoming sick.

It is, therefore, clear that only one case of hepatitis developed among 35 girls who received gamma globulin. This is obviously significant in view of the high incidence of infection both before and after the period of gamma globulin administration (Fig. 1) and the evidence provided by the April case that the infectious focus was still active. The surprising feature, of course, was the prolonged effect

35. Stokes, J., Jr.; Drake, M. E., and Capps, R. B.: The Carrier State in Viral Hepatitis, to be published.

of the gamma globulin. Twenty-one of the 35 nurses were assigned to the fourth floor six months or more after receiving the injection. This suggests the development of active immunity, perhaps because of inapparent disease during the declining phase of passive immunization. This explanation is given support by the data shown in Table 6. Thirty-one per cent of the 34 student nurses without clinical hepatitis had some laboratory evidence of liver disease. Five of 10 tested had positive skin test reactions in April, 1951. A similar situation has been previously observed and reported.[36]

COMMENT

It is believed that the nature of the epidemic among the adults has been rather conclusively established. The clinical picture, occurrence of short incubation periods, absence of a mechanism for parenteral transmission, and effectiveness of gamma globulin all indicate that we were dealing with infectious (epidemic) hepatitis transmitted by the fecal-oral or the respiratory route. The almost total absence of cases among the control maternity group eliminated water and food as a source of infection, confirmed the lack of parenteral transmission, and forced the conclusion that spread was by some type of person-to-person contact. A persistent local focus

TABLE 6.—*Evidence of Hepatitis in Student Nurses Who Received Gamma Globulin* *

	No.	No. with Positive Laboratory Data	%
Suspicious history	3	2	67.0
Negative history	32	9	28.0
Total	35	11	31.0

* One additional nurse exhibited jaundice two days after gamma globulin administration and one nine months afterward.

of infection was indicated by the definite relationship between working on the fourth floor and contracting the disease, by the eight-year duration of the outbreak, and by the prompt reappearance of the disease when gamma globulin administration was stopped. The children were proved to be infected with the virus by the demonstration of clinical, laboratory, and epidemiologic evidence of hepatitis; by the finding of cases among both nurses and children simultaneously in the same ward, and, finally, by the production of the disease in volunteers. The correlation of poor fourth-floor nursing procedure with the concentration of adult cases on this floor and the dramatic effect of the change in nursing technique demonstrated clearly that the children were the source of infection and that cross infection among nurses was not an important factor.

The high incidence of the disease in nurses on the fourth floor deserves further comment, since we have evidence that the infection was prevalent among the children on other floors as well.[15] Undoubtedly, the differences in nursing technique between floors was the critical factor, and they were sufficiently marked to provide a satisfactory answer. However, it is possible that the disease is milder and is contagious for a shorter period in younger age groups. This is suggested by the

36. Stokes, J., Jr.; Farquhar, J. A.; Drake, M. E.; Capps, R. B.; Ward, C. S., Jr., and Kitts, A. W.: Infectious Hepatitis: Length of Protection by Immune Serum Globulin (Gamma Globulin) During Epidemics, J. A. M. A. **147**:714 (Oct. 20) 1951.

fact that there were fewer demonstrable cases on the fifth floor at any one time than on the fourth floor. The reason for the rarity of the disease among the physicians and sisters was presumably that experienced persons practice aseptic technique as a matter of course; they are not as exposed to fecal contamination as student nurses, and, finally, being in an older age group, they are more likely to be immune. The "graduate" nurses, being alumnae, were presumably immune. It is perhaps strange that none of the volunteer workers acquired the disease, but such persons are usually careful about washing their hands.

As previously mentioned, the question of air-borne or respiratory transmission is still not settled. Our observations on this epidemic clearly indicate that transmission of the virus from child to nurse occurred through direct or indirect contact and that air-borne transmission did not play a role. This was demonstrated by the abrupt and complete control of the epidemic among the nurses by a simple change in nursing technique, despite adequate exposure of new girls, as well as by the correlation between the incidence of the disease and the type of nursing technique on different floors. In addition, the epidemic pattern among both the children and the nurses was not explosive in character. We believe that this study provides the first clear epidemiologic evidence against air-borne transmission in a naturally occurring epidemic in which conditions have been suitable for this form of spread. It appears probable that infection was produced entirely by the fecal-oral mechanism, although the ingestion of infected nasal secretions cannot, of course, be ruled out.

Although hepatitis without jaundice in epidemic form has been suspected among young children,[37] this is, we believe, the first time that a large number of cases has been recognized in circumstances in which the diagnosis was reasonably certain. The experimental demonstration of the virus in two cases, in addition to extensive and convincing clinical, laboratory, and epidemiologic evidence, confirms the validity of our diagnostic criteria. It is of interest that 25 of 26 patients, 96%, were not icteric. This was probably because the disease is milder in young children than in adults, possibly because some residual maternal immunity may still persist. On the other hand, in certain adult epidemics the incidence of nonicteric hepatitis may reach 90%.[2c] The epidemiologic implications are obvious.

Analysis of the student nurses who received gamma globulin suggests that in infectious hepatitis, as in other diseases, exposure during the declining phase of passive immunization may result in inapparent disease and subsequent active immunity. The problem is further discussed along with similar additional data in another report.[36] Although this approach has so far failed to be completely effective in this particular epidemic, it may prove to be more useful in other situations.

To summarize the nature of this epidemic, it would appear that infectious hepatitis has been endemic among the children for the last eight years. This endemic state was facilitated by the age group involved, by the slow turnover with continuous

37. (*a*) Cullinan, E. R.: Epidemiology of Jaundice, Proc. Roy. Soc. Med. **32**:933 (June) 1939. (*b*) Evans, P.: Comments on an Epidemic of Hepatitis, Brit. M. J. **2**:446 (Oct. 17) 1942. (*c*) Webb, C. H.; Wolfe, S. G.; Lucas, R. T., and Anderson, C. E., Jr.: Acute Hepatitis in Children: Clinical Features and Laboratory Tests, South. M. J. **40**:340 (April) 1947. (*d*) Horstmann, D. M.; Havens, W. P., Jr., and Deutsch, J.: Infectious Hepatitis in Childhood, J. Pediat. **30**:381 (April) 1947. (*e*) Cookson, J. S.: Epidemic Infective Hepatitis in Gloucestershire, Brit. M. J. **1**:687 (May 20) 1944.

addition of new susceptible persons, and by the occasional introduction of new cases. The disease was unrecognized in the absence of jaundice. The virus was passed from child to child by the fecal-oral route through handling by the nurses and also through playing together. The nurses then contracted the disease from the children by the fecal-oral route because of poor nursing technique. Proper technique alone entirely eliminated the latter spread. There was no evidence of cross infection among nurses, although occasional cases may have occurred, especially between roommates.

The epidemiologic implications of this situation to the population at large are pertinent. First, the importance of the unrecognized case of the acute nonicteric form of the disease is clearly demonstrated. Second, this disease is readily transmitted under conditions in which fecal contamination is possible. It is not unlikely that similar situations may occur more frequently than realized in other institutions where conditions are suitable. Thus, three apparently similar epidemics have been described as occurring in children's hospitals or nurseries[38] and a number in boarding schools.[39] The disease is, of course, less likely to be recognized in younger age groups because of the infrequency of jaundice.

SUMMARY AND CONCLUSIONS

An epidemic of infectious hepatitis in an orphanage for children less than 3 years of age is described. Seventy-two student nurses and three other adults were involved over a period of eight years.

Clinical, laboratory, and epidemiologic evidence of infectious hepatitis among the children was obtained. The existence of infection was proved by the production of disease in volunteers with fecal material from two children with the disease.

It was established that the nurses contracted the disease from the children. The outbreak in nurses was abolished by enforcing aseptic nursing technique alone.

Twenty-six cases of the disease were recognized in infants and children. Ninety-six per cent of the patients were without jaundice or hyperbilirubinemia. The importance of the unrecognized nonicteric case in the spread of the disease is demonstrated.

Transmission of the disease from nurse to child occurred by the fecal-oral route. Air-borne spread apparently did not occur.

Evidence was obtained that exposure to the disease during the period of declining passive immunity following administration of gamma globulin results in inapparent infection and subsequent active immunity.

Elizabeth Mills, M.S., Siu Tsien, M.S., and Virginia Morse, B.S., gave technical assistance.

38. Footnote 37*b*, *d*, and *e*.

39. Ford, J. C.: Infective Hepatitis, Lancet **1**:675 (May 29) 1943. Glover, J. A., and Wilson, J.: An Extensive Epidemic of Catarrhal Jaundice, ibid. **1**:722 (March 28) 1931. Lisney, A. A.: Epidemic Catarrhal Jaundice in School Children, Brit. M. J. **1**:703 (April 3) 1937. Pickles, W. N.: Epidemic Catarrhal Jaundice: An Outbreak in Yorkshire, ibid. **1**:944 (May 24) 1930.

INCIDENCE OF HEPATITIS AMONG NARCOTIC ADDICTS IN THE HARLEM HOSPITAL, NEW YORK

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HEPATITIS has become an important problem in the practice of medicine during the past two decades. Its incidence is increasing. Originally, attention was focused upon the liver because of damage produced by hepatotoxic agents in therapy, as well as in industry. Of the drugs and chemicals responsible for liver damage, the following may be cited: cinchophen, sulfonamides, bismuth, arsenicals, colloidal gold, quinine, and quinacrine hydrochloride (atabrine® dihydrochloride).[1] Among the industrial poisons are carbon tetrachloride, which is outstanding, trinitrotoluene, tetrachloroethylene, and phosphorus. Chloroform and ether are other chemical poisons which may act as toxic irritants on the liver.[2]

Many infections are capable of producing acute hepatic injury, i. e., virus pneumonia, infectious mononucleosis,[3] acute brucellosis, malaria,[4] and amebiasis.

During World War II a great number of cases of hepatitis appeared in epidemic form, and it was discovered that the etiological factor in many of them was a virus with a definite incubation period. In one group of cases, the incubation period of the virus was reported to be 25 to 120 days.[5] Two filtrable etiological agents have been described.[6]

It was discovered that these viruses could be transmitted in the usual manner of other organisms causing communicable diseases, i. e., gastrointestinal route,

From the Medical Service of Harlem Hospital.

1. Anderson, C. E.; Cornatzer, W. E., and Andrews, J. C.: The Role of the Liver in Metabolic Destruction of Quinine, J. Pharmacol. & Exper. Therap. **79**:62-69 (Sept.) 1943.

2. Jones, C. M.: Medical Progress: Liver Intoxication, New England J. Med. **230**:766-774 (June 22) 1944.

3. Bennett, H. D.; Frankel, J. J.; Bedinger, B., and Baker, L. A.: Infectious Mononucleosis with Hepatitis, Arch. Int. Med. **86**:391-401 (Sept.) 1950.

4. Capps, R. B.; Sborov, V. M., and Barker, M. H.: The Diagnosis of Infectious Hepatitis, J. A. M. A. **134**:595-597 (June 14) 1947.

5. Bruyn, H. B.: Homologous Serum Hepatitis Following Transfusion in Infant, J. Pediat. **31**:60 (July) 1947; abstracted, J. A. M. A. **135**:383 (Oct. 11) 1947. Murphy, H. M.: Transmission of Infectious Hepatitis by Blood Transfusions, Gastroenterology **5**:449-456 (Dec.) 1945. Rosenthal, L. T.: Four Cases of Homologous Serum Hepatitis, Gastroenterology **9**:1-17 (July) 1947.

6. Koszalka, M. F.; Lindert, M. C. F.; Snodgrass, H. M., and Lerner, H. B.: Hepatitis and Its Sequelae, Arch. Int. Med. **84**:782-797 (Nov.) 1949.

inhalation, and direct contact.[7] A particular means of transmission was found to be the direct inoculation of the blood stream through the transfusion of blood and plasma which contained the blood-borne hepatitis virus. This condition has been described as homologous serum jaundice.[6] Blood-borne virus hepatitis was also shown to be transmitted through needles, syringes, and other vessels and containers which had been infected by virus-containing blood, serum, or plasma.[8] Direct introduction into the blood stream is not always necessary. Hypodermic needles which have not been properly sterilized against the virus, even though sterilized by ordinary means against bacteria, are frequently responsible for the transmission of hepatitis.[9]

The viruses of hepatitis are resistant to the usual means of sterilization. Effective and complete sterilization against these infectious agents requires autoclaving or the use of dry heat. Boiling of 30 to 60 minutes is probably effective against the virus.[6] Irradiation of plasma, serum, or blood does not produce sterilization of the virus contamination.[10]

In the last few years narcotic addiction has become an ever-increasing problem in urban centers, particularly among teen-age boys and girls. Many of these narcotic addicts resort to the intravenous drug administration to satisfy their craving. Many problems arising from improperly sterilized needles and syringes and infected medicaments have been a consequence. Generalized sepsis and abscesses *in situ*, thrombophlebitis, syphilis, bacteremias, bacterial endocarditis, meningitis, brain and pulmonary abscesses, pulmonary embolism with or without septic infarction, and malaria[11] are not infrequent complications of this form of narcotic administration.

It occurred to us that these persons should be prone to the virus type of hepatitis because of unsanitary means of administration of drugs. While some addicts are careful in the sterilization of a syringe, the proper sterilization against virus contamination certainly is not practiced. A search was made of the records at Harlem Hospital for all inpatient admissions of narcotic addicts from 1948 to 1950. The records were also scanned for clinical and/or laboratory evidence of liver disease and jaundice, particularly hepatitis. The information from the records is not of service during the years prior to 1950. However, it is noteworthy that the number of hospital patients who were addicts has been increasing annually since 1948.[12]

7. Havens, W. P., Jr.: The Etiology of Infectious Hepatitis, J. A. M. A. **134**:653-655 (June 21) 1947.

8. Laird, S. M.: Syringe-Transmitted Hepatitis, Glasgow M. J. **28**:199-219 (Aug.) 1947.

9. Sherwood, P. M.: An Outbreak of Syringe-Transmitted Hepatitis with Jaundice in Hospitalized Diabetic Patients, Ann. Int. Med. **33**:380-396 (Aug.) 1950.

10. Rosenthal, N.; Bassen, F. A., and Michael, S. R.: Probable Transmission of Viral Hepatitis by Ultraviolet-Irradiated Plasma, J. A. M. A. **144**:224-226 (Sept. 16) 1950. James, G.; Korns, R. F., and Wright, A. W.: Homologous Serum Jaundice Associated with Use of Irradiated Plasma, J. A. M. A. **144**:228-229 (Sept. 16) 1950.

11. Applebaum, E., and Gelfand, B. B.: Artificial Transmission of Malaria Among Intravenous Diacetylmorphine Addicts, J. A. M. A. **102**:1664-1670 (May 19) 1934.

12. Altschul, A., and Foster, P. D.: Analysis of Admissions for Narcotic Addiction at Harlem Hospital, 1948-1950: A Statistical Study, Harlem Hosp. Bull., to be published.

Table 1 shows the number admitted for treatment of narcotic addiction. Table 2 shows the number of addicts admitted for treatment of conditions other than narcotic addiction.

In 1950 liver studies were inaugurated for all patients with a history of narcotic addiction, as shown in Table 1. The total number of addicts admitted for any condition will be found in either Table 1 or Table 2.

The plan of study consisted of the following:

A. Clinical demonstrations of (1) hepatitis, as manifested by gastrointestinal symptoms, nausea, vomiting, pain in the upper abdomen, jaundice, disturbances in the size of the liver, and fever, or of (2) the presence of other discernible liver disease.

B. Chemical demonstration of hepatitis in the form of blood and urinary abnormalities without the clinical manifestations and symptoms of hepatitis.

TABLE 1.—*Number of Patients Admitted for Treatment of Addiction*

	Male	Female	Total
1948	7	7	14
1949	19	5	24
1950	43	13	56

TABLE 2.—*Addicts Admitted for Treatment of Other Conditions*

1948	0
1949	0
1950	16

Of the total number of addicts admitted during the year 1950, five definitely had hepatitis; one of them died of acute yellow atrophy of the liver. An autopsy on this patient was performed by the Medical Examiner of New York County. This patient and others are described further in the detailed case reports.

REPORT OF CASES

CASE 1 (50-21468).—A. A., a 17-year-old Negro boy, was admitted to the Harlem Hospital on Nov. 20, 1950, complaining of jaundice, weight loss of 13 lb. (5.9 kg.), and anorexia of three weeks' duration. Two weeks prior to admission, the patient noticed that his sclerae were yellow. He had been addicted to diacetylmorphine hydrochloride (heroin), which he sniffed up to three weeks prior to admission. Shortly before his admission, however, he had given himself an intravenous injection of diacetylmorphine with a syringe which had been used by each of several persons for inoculation and without intermediate sterilization. The patient denied chills, fever, or any type of abdominal pain. He also denied changes in the color of his stools or urine. The past history and family history were not contributory.

Physical examination revealed a well-developed, well-nourished Negro boy not in acute distress. He had jaundice, particularly noticeable in the sclerae. The results of the ear, nose, and throat examination were not unusual. The mucous membrane of the mouth was tinted yellow. The lungs were clear to percussion and auscultation. The heart was not enlarged; it had a normal, regular rhythm, with a rate of 72 a minute. No murmurs were heard. The abdomen was flat; the liver was palpable 2 fingerbreadths below the costal region and was slightly tender. The spleen and kidneys were not felt; no other masses were palpable. The extremities showed

no edema or varicosities. The rectal examination revealed no abnormality except for light fecal material on the glove. The urine was dark. The temperature was normal. The liver was enlarged down to 3 fingerbreadths and was tender on Nov. 27. There was severe icterus. Urinalysis on Nov. 21 showed the specific gravity to be 1.015; the reactions for albumin and sugar were negative. Bile was present, and urobilinogen was noted in 1:50 dilution. Microscopic study showed crystals (2+) which were reported to be of sulfadiazine. The patient, however, gave no history of having received any sulfonamide preparation. Blood chemical examinations disclosed 1.3 mg. of creatinine, 8 mg. of urea nitrogen, 76 mg. of glucose, 4.80 gm. of albumin, and 2.50 gm. of globulin, with total protein measuring 7.30 gm., per 100 cc. The albumin to globulin ratio was 2.30. A blood Kahn reaction on Nov. 22 was negative.

On Nov. 27 chemical examinations revealed the icterus index to be 100. The van den Bergh test gave a direct immediate reaction. Cephalin flocculation was 4+ in 24 hours. On Dec. 1 blood amylase measured 62 Somogyi units.

On Dec. 4 the patient was nauseated and vomiting and complained of headaches. A peculiar odor described as fetor hepaticus was noted. The icterus index was 132, and the van den Bergh test gave the same results as on Nov. 27. Cephalin flocculation was 4+ in less than 24 hours.

Increased weakness, malaise, and anorexia and nausea relieved by vomiting were noted on Dec. 5. The abdomen was tense and appeared moderately distended. No free fluid was detected. The liver was still 3 fingerbreadths below the costal border and was tender. The patient was depressed and drowsy. Liver extract was given, and fluids with dextrose and vitamin B complex were administered parenterally. No further amino acids were detected in the urine. The peculiar fetor was still present. The clinical diagnosis was acute yellow atrophy of the liver with impending cholemia.

Blood studies on Dec. 8 disclosed 1.3 mg. of creatinine, 8 mg. of urea nitrogen, and 50 mg. of glucose. The urine was acid, with a specific gravity of 1.015. A negative reaction for sugar and a 1+ reaction for albumin were obtained. Microscopically many hyaline and granular casts and uric acid crystals were seen.

The patient was kept in bed and given intravenously 1,000 cc. of protein hydrolysates (amigen®) and later 250 cc. of plasma, dextrose and distilled water, and concentrated dextrose solution.

On Dec. 9 the patient was comatose and exhibited no response to previous therapy. The blood was reported as showing 9% eosinophiles. Corticotropin (ACTH) was given in doses of 25 mg. every six hours. A second blood count failed to show eosinophiles. The patient was still comatose, with widely dilated pupils reacting to light. All extremities were mobile. Involuntary micturition occurred.

The patient went into deep coma on Dec. 10, with Cheyne-Stokes respiration and diffuse rhonchi in both sides of the chest. Aminophylline and concentrated dextrose solution were given intravenously. The patient died at 7:30 p.m.

The autopsy was performed on Dec. 12 by Dr. Henry Weinberg, Assistant Medical Examiner for the City of New York. He reported the diagnosis to be acute yellow atrophy of the liver, following intravenous injections of diacetylmorphine hydrochloride, and chronic drug addiction.

CASE 2 (50-19324).—An 18-year-old Negro boy, E. L., was admitted to the Harlem Hospital on Oct. 18, 1950, because of abdominal discomfort. This came on in the late afternoon and in the evening and was relieved by drinking milk. He denied hematemesis, tarry stools, or change in his bowel habits. The patient had been taking diacetylmorphine hydrochloride intravenously for approximately one month prior to admission to the hospital. The past history was noncontributory.

Physical examination revealed a young man with poor nutrition who was restless. Examination of the head, eyes, ears, nose, and throat showed no abnormalities. The chest was clear to percussion and auscultation. The heart was not enlarged, with regular rhythm and no murmurs. The blood pressure was 110/70. The abdomen was scaphoid, with paraumbilical tenderness but no rebound. The antecubital fossae showed needle punctures. The urinalysis on admission revealed a 4+ reaction for glucose and a 1+ reaction for ketones; the fasting blood sugar was 375 mg. per 100 cc. A van den Bergh test on Oct. 17 showed a direct immediate reaction. The icterus index

was 17 and cephalin flocculation 2+. On Oct. 26 there was a slight icteric tint to the sclerae. On Oct. 30 albumin measured 3.92 gm., globulin, 2.33 gm., and total protein, 6.25 gm., per 100 cc. The albumin to globulin ratio was 1.68. Alkaline phosphatase was 11.4 Bodansky units.

The patient was given a diet of 150 gm. of carbohydrate, 70 gm. of protein, and 70 gm. of fat. This later was increased to 200 gm. of carbohydrate, 80 gm. of protein, and 80 gm. of fat. At first additional insulin was prescribed to cover the increased carbohydrate intake. Eventually the patient received 30 units of protamine zinc insulin and 80 units of regular insulin with fair control. The abdominal symptoms cleared with bed rest, and carbohydrate and insulin administration. In addition, the patient took extra food which his friends brought him, so that diabetic control was somewhat delayed and difficult. His blood sugar varied between 375 mg. on admission and 80 mg. on discharge.

On Nov. 15 the icterus index was still 15 mg. per 100 cc. The van den Bergh test gave a direct immediate positive reaction. Cephalin flocculation was now normal.

He was discharged Dec. 1, 1950, to the outpatient department with instructions to take a high-carbohydrate diet and supplementary vitamins.

Case 3 (50-17292).—H. G., a 20-year-old Negro man, was admitted to the Harlem Hospital Sept. 15, 1950. His chief complaint was yellow discoloration of the eyes. The past history included measles and jaundice at the age of 3 years, with recurrent attacks of colds and weight loss during the past year. The patient had received injections of diacetylmorphine intravenously for one year. In February, 1950, he had discontinued the use of the narcotic for one month. Four days prior to admission he experienced generalized malaise. The next day he had abdominal cramps and pain in the right upper abdominal quadrant, together with vomiting after each meal. On the day of admission the yellow discoloration was generalized.

Physical examination revealed a fairly well-developed and well-nourished Negro man. The sclerae were icteric. The pupils were round, regular, and equal and reacted to light and accommodation. The ears and nose were normal. The pharyngeal mucosa was slightly congested. The lungs were clear to percussion and auscultation. The heart sounds were regular and of good quality. The aortic second sound was greater than the pulmonary second sound. There were no murmurs. The blood pressure was 120/80. The abdomen and genitalia were not unusual, except for needle scars in the antecubital fossae. The patient supplied the additional information that on numerous occasions of narcotic administration the syringe was passed from one person to another.

On Sept. 18 blood creatine measured 1.3 mg., urea nitrogen, 8 mg., and sugar, 60 mg., per 100 cc. On the eighth day the jaundice cleared. Studies on Oct. 2 showed 4.5 gm. of albumin, 2.55 gm. of globulin, a total of 7.05 gm. of protein (albumin-globulin ratio, 1.76), and an icterus index of 14. The van den Bergh reaction was negative; cephalin flocculation was 3+, and alkaline phosphatase, 2.6 Bodansky units. On Oct. 25 albumin was 4.27 gm. and globulin 3.18 gm., a total protein of 7.45 mg., per 100 cc. The albumin to globulin ratio was 1.34. Alkaline phosphatase was 3.8 Bodansky units. The icterus index was 9.8. A negative reaction was obtained on the van den Bergh test, and cephalin flocculation was 2+. On Oct. 28 the icterus index was 22. A direct immediate reaction resulted on the van den Bergh test, and cephalin flocculation was normal.

A chest roentgenogram taken on Sept. 15 revealed calcified hilar nodes, but no active tuberculosis. A roentgen examination on Sept. 19 showed the lumbosacral portion of the spine to be normal. There was a low-grade fever for six weeks which then subsided. The patient's condition improved in general. During his stay in the hospital his temperature ran a course from 97 to 100 F.

Case 4.—J. R., a 28-year-old Negro man, was admitted to the Harlem Hospital Feb. 10, 1950, because of icteric sclerae. For four days prior to admission he had had postprandial vomiting or emesis. This was accompanied with chills, fever, anorexia, and diarrhea. Four days prior to admission he noticed light-colored stools. Two days later he noticed yellowness of the eyes. Three months prior to admission he had become addicted to diacetylmorphine hydrochloride. The means of administration was hypodermic injection twice daily. One and a half years before this illness a positive Wassermann reaction was discovered, because of which he had received treatment for six months. Two of his brothers suffered from tuberculosis.

Physical examination revealed a cooperative well-developed, well-nourished Negro man not in acute distress. The sclerae were icteric. The pupils reacted to light and accommodation. The ears, nose, and throat were normal. The lungs were clear to percussion and auscultation. The heart showed the point of maximum impulse in the fifth intercostal space in the nipple line. The rhythm was regular; the rate was 88 per minute, and no murmurs were noted. The blood pressure was 122/74. The abdomen was not tender, but the liver edge was felt 1½ fingerbreadths below the right costal margin. The genitalia and extremities were normal.

On Feb. 14 the urine showed a specific gravity of 1.015. It had an alkaline reaction. The reactions for sugar, albumin, and bile were negative. Urobilinogen (3+) was noted. Triple phosphate crystals were observed in the sediment. On Feb. 15 creatinine measured 1.3 mg., urea nitrogen, 8 mg., and glucose, 85 mg. per 100 cc. The icterus index was 27. The van den Bergh reaction was direct and immediate. Cephalin flocculation was normal. Alkaline phosphatase was 12.1 Bodansky units. Serum globulin measured 2.75 gm., serum albumin, 4.40 gm., and total protein, 7.15 gm., per 100 cc. A roentgenogram of the chest was normal.

The subsequent clinical course was uneventful. The icteric sclerae cleared. The temperature varied between 88 and 100 F. rectally. The patient was given protein hydrolysates (amigen®) intravenously, 10% dextrose in distilled water, vitamins parenterally, and a high-protein, high-carbohydrate, low-fat diet. After 27 days the patient was discharged.

Further laboratory studies on March 3 showed the specific gravity of the urine to be 1.014. The reactions for sugar and albumin were negative. The reaction for bile was positive. The Kahn test had a 2+ reaction. On March 6 the icterus index was 22. Cephalin flocculation was normal. On March 8 albumin was 4.40 gm., globulin was 2.78 gm., and total protein was 7.18 gm., per 100 cc. Alkaline phosphatase was 9.3 Bodansky units. Tests for heterophile amboceptor and agglutination for Weil's disease gave normal results.

CASE 5 (50-20438).—O. H., a 38-year-old Negro man, was admitted to the Harlem Hospital Nov. 5, 1950, with the chief complaint: "I have liver trouble." This illness began nine days prior to admission with postprandial vomiting. The following day he noted light-colored stools and a bad taste in his mouth. The urine was light to dark green. Two days later fever developed.

Physical examination revealed a well-developed, well-nourished Negro man not in acute distress. The sclerae were clear, and the pupils reacted to light and accommodation. The ears, nose, and throat were normal except for hypertrophied tonsils. The heart was enlarged, with regular rhythm and a Grade I apical systolic murmur. The aortic second sound was louder than the pulmonary second sound. The lungs were clear. The blood pressure was 128/90. There was tenderness in the right upper abdominal quadrant, with the liver palpable 2 fingerbreadths below the right costal border. The spleen and kidneys were not felt. The genitalia and extremities were not unusual, and the results of neurologic examination were essentially normal. On the second hospital day the patient admitted being addicted to diacetylmorphine hydrochloride. He had been in the San Francisco Hospital, San Francisco, seven days because of a generalized maculopapular hyperemic lesion. This developed after an intravenous injection of diacetylmorphine.

Upon discharge from the San Francisco Hospital, he came to New York. Two weeks later the present illness began. One examiner noticed icteric sclerae. The patient's temperature varied between 97 and 101 F. (rectum). He was given a high-protein, high-carbohydrate, low-fat diet supplemented by high-vitamin intake and infusions of 10% dextrose solution, with parenteral administration of vitamins and choline.

On Nov. 6 urea nitrogen measured 15.1 mg., glucose, 80 mg., and creatinine, 1.3 mg., per 100 cc. of blood. Alkaline phosphatase was 7.9 Bodansky units. Albumin was 4.5 gm., globulin, 2.75 gm., and total protein, 7.25 gm., per 100 cc., on Nov. 15. The albumin to globulin ratio was 1.47, and alkaline phosphatase was 6.5 Bodansky units.

On Nov. 22 albumin was 4.30 gm., globulin, 2.7 gm., and total protein, 7.00 mg., per 100 cc. The albumin to globulin ratio was 1.59. Studies on Dec. 1 showed the icterus index to be 8. The van den Bergh reaction was negative. Serum amylase was 45 Somogyi units and cephalin flocculation 2+. On Dec. 4 the icterus index, van den Bergh reaction, and cephalin flocculation were the same as on Dec. 1.

The patient was discharged as improved 34 days after admission. The diagnosis of hepatitis and addiction to diacetylmorphine hydrochloride was made. This diagnosis was based on the findings of icteric sclerae, abnormal cephalin flocculation (2+), enlargement of the liver, and upper abdominal pain.

COMMENT

From the histories obtained from these patients, the intravenous self-administration of narcotics occurred 21 to 90 days before the onset of symptoms. However, one cannot rely upon these figures for accuracy. Narcotic addicts are not always truthful, particularly when admission of onset of the addiction is involved.

Patient 1, on whom there was an autopsy report of acute yellow atrophy of the liver, was an adolescent, 17 years of age, who definitely received diacetylmorphine hydrochloride intravenously. This was given three weeks prior to admission. Patient 2 admitted taking diacetylmorphine hydrochloride one month prior to admission to the hospital. Patient 3 had been taking diacetylmorphine hydrochloride intravenously for one year prior to admission, so that it is difficult to place his onset. The hospital findings showed hepatitis, which, in all probability, was due to intravenous administration of the drug.

Patient 4 became addicted to diacetylmorphine hydrochloride three months prior to admission to the hospital. He received a hypodermic injection twice daily. In this patient there was no specific evidence of intravenous administration. Although the cephalin-flocculation reactions were normal, the clinical picture and other laboratory evidence indicated hepatitis.

Patient 5 had a positive cephalin-flocculation reaction, with low-grade elevation of the icterus index. While there was no visible jaundice, the liver was enlarged and fever was also present. One of the examiners noted icterus. This patient had been taking diacetylmorphine hydrochloride intravenously for at least three months prior to admission to the hospital.

In all five patients with narcotic addiction there was definite evidence of liver damage and icterus. Four of these patients were addicted to intravenous use of diacetylmorphine. One patient may have had such an addiction but took the drug subcutaneously. He also showed evidence of liver damage and hepatitis.

The drug obtained by addicts is frequently adulterated and "stretched" with lactose and other substances. The possibility that the adulterant might act as a liver irritant is minimal.

Information received from practicing physicians in the area served by Harlem Hospital confirms the sudden increase in cases of jaundice among diacetylmorphine and other narcotic addicts during the late summer and fall of 1950. It is, therefore, plausible that many others who used the same syringe as did these five patients admitted to Harlem Hospital probably had hepatitis and contracted the disease in the same manner.

It is not unreasonable to expect virus hepatitis as a complication of intravenous narcotic administration. Since the inauguration of this study at Harlem Hospital, Steigmann, Hyman, and Goldbloom have reported 23 cases of infectious hepatitis in drug addicts.[13] The importance of this complication becomes even

13. Steigmann, F.; Hyman, S., and Goldbloom, R.: Infectious Hepatitis (Homologous Serum Type) in Drug Addicts, Gastroenterology **15**:642-646 (Aug.) 1950.

greater as both a medical and a criminological problem. Addiction itself is a serious condition, but the complication of hepatitis must be kept in mind by members of the medical profession in order to avoid widespread dissemination of hepatitis among innocent persons by incomplete sterilization of syringes, needles, and containers in physicians' offices and institutions.

SUMMARY

Five cases of hepatitis are reported in narcotic addicts. All used diacetylmorphine hydrochloride (heroin).

Four patients employed the intravenous route. One patient used the hypodermic route. Four patients were jaundiced, and one patient had other evidence of hepatitis without definite jaundice. Improper sterilization of syringes, needles, and the drug itself existed in all five cases.

Lenox Ave. and W. 136th St.

USE OF CORTICOTROPIN AND CORTISONE IN ACUTE HOMOLOGOUS SERUM HEPATITIS

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THE ABILITY of the physician to treat liver disease on any rational basis has probably made little progress in the last century.[1] The doctor's resources in the therapy of acute hepatitis include rest in bed, forced high-protein and high-carbohydrate intake, administration of lipotropic agents, liver extract, and multiple vitamins, and parenteral fluid alimentation, including use of salt-poor albumin.[2] With early diagnosis and institution of therapy, many patients will recover from the acute stage of the disease. Experience has demonstrated, however, that a number of these patients will die of an acute rapidly progressive hepatitis and cholemia. These patients usually become anorectic, with severe nausea and vomiting. Parenteral alimentation becomes difficult, especially when the patient is confused and disoriented. It is imperative, therefore, to obtain some agent which will provide support until the liver can repair itself. Eppinger in Europe [3] and recently Webster [4] in this country have utilized adrenal cortex extract in an attempt to alter the metabolism of carbohydrates and protein and thus protect the liver and encourage healing. Finland,[5] in studying the effects of corticotropin (ACTH) in pneu-

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1. Watson, C. J.: The Prognosis and Treatment of Hepatic Insufficiency, Ann. Int. Med. **31**:405 (Sept.) 1949.

2. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J. Clin. Invest. **20**:48 (Sept.) 1941. Patek, A. J., Jr.; Merkin, H.; Lowell, A., and Earle, D. P., Jr.: The Effect of Intravenous Injection of Human Serum Albumin upon Blood Plasma, Ascites and Renal Functions in 3 Patients with Cirrhosis of the Liver, J. Clin. Invest. **27**:135 (Jan.) 1948.

3. Eppinger, H.: Die Leberkrankheiten: Allgemeine und spezielle Pathologie und Therapie der Leber, Wien, Julius Springer, 1937.

4. Webster, J. J.: Adrenal Cortex in Liver Disease, Ann. Int. Med. **33**:854 (Oct.) 1950.

5. Finland, M.; Kass, E. H., and Ingbar, S. H.: Effects of ACTH in Primary Atypical (Viral) Pneumonia and in Pneumococcal Pneumonia, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 529.

moccocal and viral pneumonias, noted marked psychic stimulation, with defervescence and relief of symptoms and signs of toxemia in all his cases, but with no evidence of bactericidal or virucidal action exerted by the adrenal steroids. Similar observations have been reported on patients with active pulmonary tuberculosis.[6] We have recently had experience with four cases of acute homologous serum hepatitis in which, in spite of the use of accepted methods of therapy, the course rapidly went downhill. In view of the known effects of corticotropin and cortisone in producing a sense of well-being, euphoria, and increase in appetite and food intake, with resultant increase in deposition of glycogen in the liver, these patients were given corticotropin or cortisone. Prompt clinical remission occurred. The present report is an analysis of this group.

REPORT OF CASES

CASE 1.—F. I. (52318), a 66-year-old white man, had had cystectomy and bilateral ureterosigmoid implantation four months prior to hospital admission. During the immediate postoperative period the patient received 4 liters of blood. Three months later he exhibited nausea, bouts of vomiting, and a low-grade fever, for which he was admitted to Montefiore Hospital in January, 1950. Physical examination revealed a well-developed, well-nourished white man in no acute distress. The tongue was beefy red. The blood pressure was 100/80. The lungs revealed fine moist rales at the right upper lobe anteriorly. There was no icterus. The liver was nontender and was situated 3 cm. below the right costal margin. The spleen was not felt. The results of the remainder of the physical examination were normal.

Laboratory studies on admission revealed a hemoglobin concentration of 11.5 gm. and a white blood cell count of 11,900, with a normal differential count. Fasting blood sugar was 93 mg., blood urea nitrogen 34 mg., creatinine 1.3 mg., and total protein 7.1 gm., with 4.2 gm. of albumin and 2.9 gm. of globulin, per 100 cc. Thymol turbidity was 9 units; cephalin flocculation was 4+; the prothrombin time was within normal limits. A roentgenogram of the chest revealed old fibrocalcific tuberculosis involving the right upper lobe. A roentgenographic series of the gastrointestinal tract was normal. The electrocardiogram was within normal limits. On urinalysis, the specific gravity could not be obtained because of the ureterosigmoidostomy; otherwise no abnormalities were noted.

Hospital Course.—The patient's initial anorexia and vomiting improved with parenteral administration of fluids and vitamins so that during the second week he took food by mouth. The diagnosis, in view of the physical findings and chemical abnormalities, was low-grade homologous serum hepatitis. After the second week he became gravely ill, drowsy, and anorectic and vomited constantly. Icterus appeared and rapidly deepened; there was progressive liver enlargement. The bilirubin rose to 14.5 mg. per 100 cc. by the 28th hospital day. Corticotropin therapy in doses of 60 mg. per day was begun. Within 36 hours, there was a complete loss of all gastrointestinal symptoms and a voracious appetite set in. Corticotropin was given for a total of 28 days, during which well-being was maintained except for a 2-day period when temporary cessation of the corticotropin treatment resulted in relapse of nausea and vomiting. Icterus diminished steadily with amelioration of the clinical state. Several days after the permanent withdrawal of corticotropin treatment, a recurrence of mild anorexia and lagging appetite made it necessary to resume supportive therapy, this time with cortisone in doses of 100 mg. every other day. On the 96th hospital day the patient was discharged, having made a complete clinical recovery. The cephalin flocculation had fallen to 1+; thymol turbidity, to 5 units, and serum bilirubin, to 1.0 mg. per 100 cc. (Fig. 1).

Comment.—This patient presented a low-grade homologous serum hepatitis which, in spite of complete rest in bed and fair dietary intake, suddenly developed an acute acceleration with

6. Freeman, S.; Pershing, S.; Wong, C. C., and Smith, L. C.: The Effect of ACTH on Patients with Pulmonary Tuberculosis, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 509.

rapid deterioration. The institution of corticotropin therapy produced a remarkably rapid improvement. On cessation of the hormone administration, there was an immediate relapse, which was corrected, however, on restoration of therapy.

CASE 2.—B. K. (54617), a 31-year-old white woman, was admitted to Montefiore Hospital with the chief complaint of jaundice of five days' duration. In August, 1950, the patient had a panhysterectomy for a uterine fibroid and received 500 cc. of whole blood during this operation. Four weeks postoperatively the patient had hot flashes and became quite apprehensive. She was given estrogens by mouth and parenterally, with relief of symptoms. Six weeks postoperatively, the patient noticed the insidious onset of epigastric distress, anorexia, nausea, and easy fatigability with fever. These symptoms persisted, and on Oct. 26 the patient noted that her skin had become icteric, her urine dark, and her stools light. She was admitted to Montefiore Hospital on Oct. 30, with a diagnosis of homologous serum hepatitis. Physical examination revealed the patient's temperature to be 99 F., the pulse rate, 80, the respiratory rate, 20, and the blood pressure, 115/80.

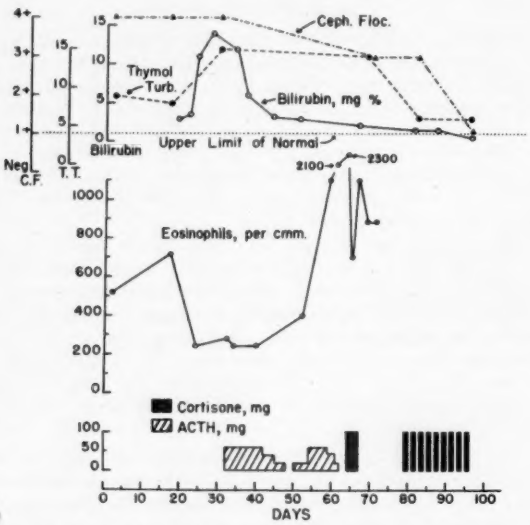

Fig. 1 (Case 1).—Course of acute homologous serum hepatitis in patient receiving corticotropin (ACTH) and cortisone therapy. *C. F.* means cephalin flocculation, and *T. T.*, thymol turbidity.

The patient appeared well nourished and mildly icteric and complained of nausea and flatulence. Examination of the heart and lungs revealed nothing abnormal. A moderately tender liver could be palpated just at the right costal margin. The spleen could not be felt.

The laboratory data were as follows: Blood studies showed 3,800,000 red blood cells, a hemoglobin concentration of 11 gm., and 4,400 white blood cells, with a differential count of 55% segmented forms, 23% lymphocytes, 2% eosinophils, and 9% monocytes. Urine examination revealed no reactions for albumin or sugar. The sediment showed no cells or casts. The reaction for bile was positive, and urobilinogen was present in 1:10 dilution. The erythrocyte sedimentation rate was 10 mm. in one hour (Cutler method). Blood urea nitrogen was 14 mg., fasting blood sugar 86 mg., and total serum bilirubin 4.1 mg., per 100 cc. The cephalin flocculation was 4+; thymol turbidity, 18 units; alkaline phosphatase, 3.1 Bodansky units, and total serum proteins, 7.7 gm., with 4.7 gm. of albumin and 3.0 gm. of globulin, per 100 cc.

Course.—Therapy consisted of complete rest in bed, a high-protein, 3,000-calorie diet, and administration of choline, vitamins, and intravenous infusions of dextrose solution. During the

first two weeks, initial improvement was observed and the total serum bilirubin fell to 1.7 mg. per 100 cc. The patient was allowed up in a chair for three days. After this activity, the patient became nauseated, had pain and tenderness in the right upper abdominal quadrant, and became more icteric. Strict rest in bed was reinstituted, and dextrose infusions and vitamin injections were added to the therapeutic regimen. Despite rigorous dietary treatment, the patient's condition became progressively worse.

Corticotropin treatment was started on the 19th hospital day. Over a five-day period, the patient received 430 mg. of corticotropin. By the third day of treatment the appetite improved and the patient exhibited a sense of well-being. Corticotropin therapy was stopped because of the patient's objection to the injections. Three days later, the patient again became anorectic and nauseated and complained of pain in the right upper abdominal quadrant. The liver was easily palpable 1 fingerbreadth below the right costal margin. A second course of corticotropin therapy was started on the 29th day. Over a 13-day period, the patient received 620 mg. of corticotropin. Toward the end of this course, her symptoms became worse and icterus increased. The eosinophil count rose to 462 per cubic millimeter. Corticotropin therapy was stopped at this time. In the next week the patient became markedly depressed and nauseated and complained of persistent pain in the right upper abdominal quadrant. Vomiting shortly appeared, and severe drowsiness, progressing to stupor, became evident. The liver was now palpable 2 fingerbreadths below the right costal margin, and the total serum bilirubin rose to 22 mg. per 100 cc. The results of liver-function tests remained markedly abnormal. Rather profuse bleeding began from her nose and gums, associated with an elevated prothrombin time. On the 47th hospital day, corticotropin therapy was again reinstituted (in doses of 100 mg. per day). The eosinophil count promptly fell to 0. Within three days marked clinical improvement was noted. Vomiting disappeared; appetite returned, and she became much more aware of her surroundings. The right upper quadrant pain decreased, although the liver increased in size to 3 fingerbreadths below the right costal margin. By the end of the first week of this course of therapy, a moon-shaped facies with acne appeared for the first time. Administration of 6 gm. of potassium citrate daily was started. Improvement was progressive. Serum levels of sodium, potassium, carbon dioxide, and chloride remained within normal limits. Despite good caloric intake the patient gained only 4 lb. (1.8 kg.) and did not display clinical edema. The urine output ranged between 1 and 2 liters daily. During corticotropin therapy, transient glycosuria occurred but with normal blood sugar levels. The amount of corticotropin given was gradually decreased, and its use was discontinued on the 71st day. In 25 days 2,000 mg. of corticotropin had been administered (Fig. 2).

On cessation of corticotropin therapy, clinical improvement was maintained and the patient became more cheerful. By the 85th day the serum bilirubin had fallen to 4.3 mg. per 100 cc. Facial acne and rounding gradually disappeared. The liver remained palpable 2 fingerbreadths below the right costal margin and was firm and nontender. In spite of clinical well-being, cephalin flocculation remained 3+ and the sedimentation rate was elevated. By the 100th day, the tip of the spleen became palpable and it was evident that the patient still had active chronic hepatitis. This opinion has been borne out by her subsequent course.

Comment.—This 31-year-old white woman, who underwent surgical menopause, displayed symptoms and signs of homologous serum jaundice after blood transfusion. After initial improvement with the usual medical regimen, there rapidly developed the clinical picture of acute hepatic parenchymal decompensation. Because of the progressive nature of the illness despite rigorous treatment, it was felt that this patient's condition represented a case of fulminating hepatitis. Corticotropin therapy was started. Because of a lack of previous experience with the agent in treatment of this disease, two courses were given cautiously. With the cessation of the second course of corticotropin administration, there was a grave exacerbation, including hemorrhagic episodes and stupor. In view of impending hepatic coma and experience recently acquired in management of Case 1, it was decided to reinstitute corticotropin therapy. The rising eosinophil count with moderate doses of corticotropin suggested an inadequate adrenocortical discharge. Accordingly, larger doses were given, with a prompt fall of eosinophils to 0 and a concomitant gradual clinical improvement. The third course consisted of 2,000 mg. of corticotropin administered over a 25-day period. Although clinical improvement was striking, evidence of continuing active hepatitis was present in the form of an elevated cephalin-flocculation reaction and sedi-

mentation rate. Accordingly, the patient was kept on a strict dietary regimen and at rest in bed. The subsequent course of this patient bore out the suspicion of active disease when she relapsed 6 weeks after cessation of corticotropin therapy and 17 weeks after onset of illness.

CASE 3.—M. K. (56121), a 50-year-old white housewife, was first admitted to Montefiore Hospital on Jan. 19, 1951, because of progressive anorexia and malaise of two weeks' duration; nausea, vomiting, and jaundice of one week's duration prior to admission, and persistent aching pain in the right upper abdominal quadrant for 48 hours.

The past history revealed that she had received two whole-blood transfusions in October, 1950, during left radical mastectomy for neoplasm.

On admission the patient was moderately obese and icteric, with a temperature of 100 F. and a blood pressure of 134/80. There was no significant lymphadenopathy. The heart and lungs were normal. There was a radical mastectomy scar on the left without evidence of local recur-

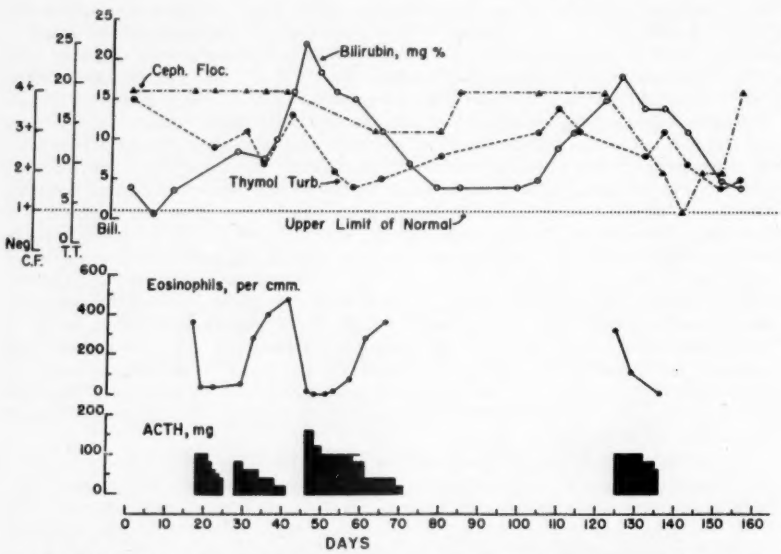

Fig. 2 (Case 2).—Course of acute homologous serum hepatitis in patient receiving corticotropin (ACTH). In this patient the disease progressed to an active chronic hepatitis.

rence of the neoplasm. The liver was tender and palpable 2 fingerbreadths below the right costal margin. The spleen was not felt. Results of the remainder of the physical examination were unremarkable. The blood urea nitrogen and fasting blood sugar levels were within normal limits. The thymol turbidity was 25 units; cephalin flocculation was 4+; serum alkaline phosphatase was 3.4 Bodansky units; serum bilirubin was 23.5 mg. per 100 cc. The urine gave a positive reaction for bile but otherwise was unremarkable. The patient's early hospital course was marked by increasing anorexia, nausea, and frequent episodes of vomiting and low-grade fever. She became deeply icteric; the abdomen was distended, and the liver rapidly enlarged to 4 to 5 fingerbreadths downward. The spleen became palpable. Despite daily dextrose and vitamin infusions she became increasingly anorectic and irritable.

On the 15th hospital day corticotropin administration was begun in a dose of 25 mg. every six hours. There was a prompt fall in eosinophils. Within 48 hours there was a dramatic alteration of her course. She ate breakfast for the first time with "a little appetite." She was alert, cooperative, and anxious to get out of bed. Within a week there was visible lessening of the

icterus. Her temperature returned to normal, and an excellent appetite and good intake were maintained. Corticotropin dosage was gradually lowered. There was a progressive diminution in the hepatosplenomegaly, so that by the 31st day the liver was palpable only 2 fingerbreadths and the spleen a bare 1 fingerbreadth. The eosinophil count rose progressively. By the 49th day the corticotropin treatment was stopped. The liver was now palpable only on deep inspiration and was not tender. There was no splenomegaly and only barely perceptible scleral icterus. The patient was allowed to sit in a chair for a few hours each day without any exacerbation. On the 50th hospital day, the serum bilirubin was 0.5 mg. per 100 cc.; thymol turbidity was 4 units, and cephalin flocculation, 2+. Clinically, she appeared completely recovered (Fig. 3).

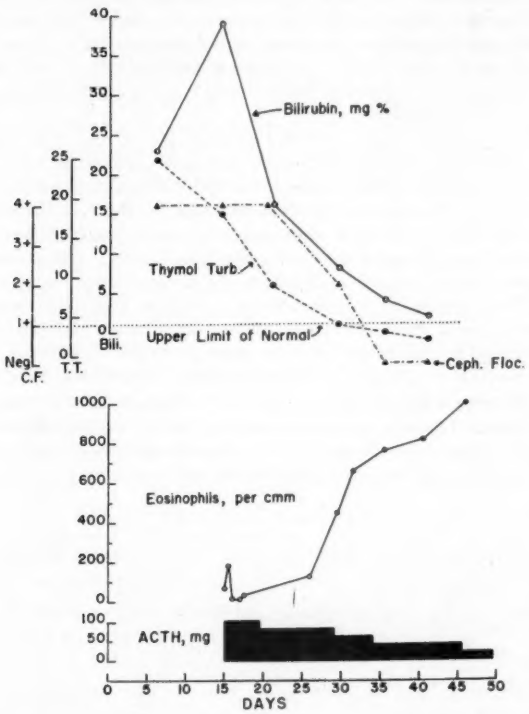

Fig. 3 (Case 3).—Course of acute homologous serum hepatitis in patient receiving corticotropin (ACTH) therapy.

Comment.—This patient presented a picture of progressive hepatic failure, both clinically and biochemically. In spite of good hydration, lethargy and drowsiness soon appeared, which suggested the possibility of impending hepatic coma. At this time there was no evidence of azotemia. Corticotropin therapy was begun at this stage, and within 48 hours a remarkable improvement occurred, manifested by clearing of the sensorium, a sense of well-being, and a good appetite. Concomitantly, there was a fall in serum bilirubin and thymol turbidity. The prompt eosinophil fall indicated a good adrenal response. After two weeks of treatment with the corticotropin, and while the dose was gradually reduced, there was a marked rise in eosinophils but with maintenance of clinical improvement. Corticotropin treatment was discontinued after three weeks, without recurrence of signs or symptoms.

CASE 4.—J. S., a 48-year-old white man, had an exploratory laparotomy on Oct. 7, 1950, at which time a retroperitoneal lymphosarcoma without visible metastases to the liver was found. At this time, he received 2 liters of blood. On Dec. 5, 1950, he was seen by his attending physician, complaining of weakness and of having passed dark urine for two weeks. Physical examination revealed deep icterus of the scleras and skin. The liver was palpable 3 fingerbreadths below the right costal margin and was tender. The spleen was not palpable. The urine showed the presence of bile. Cephalin flocculation was 4+; thymol turbidity, 7 units; alkaline phosphatase, 7 Bodansky units, and serum bilirubin, 8.1 mg. per 100 cc. The prothrombin time was slightly prolonged. A gall-bladder study revealed no calculi. It was the impression of the attending physician that the patient had early homologous serum hepatitis. A regimen of complete rest in bed, with an oral intake of approximately 2,800 calories per day and administration of multiple vitamins, lipotropic agents, and a vitamin K preparation orally, was instituted. On Dec. 19, the patient refused to eat and began to complain of severe nausea and vomiting. He was markedly depressed. The icterus became progressively deeper. The serum bilirubin was 23 mg. per 100 cc.; alkaline phosphatase, 7 Bodansky units; cephalin flocculation, 3+, and thymol turbidity, 70 units. The patient rapidly became semistuporous.

In view of the experience gained from the previous cases, it was decided to try adrenal steroid therapy. Accordingly, 100 mg. of cortisone was given parenterally, and within 24 hours there was definite clinical improvement, manifested by return of appetite and a sense of well-being. Cortisone administration was continued in the same dosage for the next four days. After this, the patient was maintained on 50 mg. of cortisone per day for 72 hours. At the end of this time the liver receded to 1 fingerbreadth below the right costal margin, with diminution of gross icterus. Eleven days following cessation of therapy, the serum bilirubin had fallen to 3 mg. per 100 cc.; alkaline phosphatase, to 4 Bodansky units; cephalin flocculation, to 0, and thymol turbidity, to 5 units. Serial studies revealed a constant fall in serum bilirubin to normal levels. At the present writing, the patient appears to be completely recovered. The liver is not palpable. There has been a marked weight gain, and serum bilirubin is now 0.5 mg. per 100 cc.

Comment.—This case is included in our series as one of moderately severe homologous serum hepatitis that responded favorably to cortisone treatment. It was the impression of the attending physician that the patient's clinical condition was critical at the time of institution of hormone therapy. Striking clinical and laboratory improvement was noted after use of this hormone.

GENERAL COMMENT

A series of four cases is certainly too small to be of any statistical significance. It is of interest, however, that the courses of all the patients were rapidly going downhill, in spite of fair food intake and parenteral administration of vitamins and liver extract. These patients uniformly showed a remarkable clinical change following the administration of corticotropin. Liver-function studies all disclosed a definite improvement, and in some cases the results reverted to normal in a remarkably short time. This is in marked contrast to the persistent elevation of the thymol-turbidity and cephalin-flocculation reactions seen in many patients long after they have shown clinical improvement with the usual therapeutic regimen.

The exact mode of action of corticotropin in these patients with acute hepatitis is difficult to ascertain. On the basis of studies in viral and bacterial pneumonia,[5] pulmonary tuberculosis,[3] poliomyelitis,[7] and mouse and ferret influenza,[8] there is no

7. Coriell, L. I.; Murphy, L.; Siegel, A. C.; Stokes, J., Jr., and Cook, C. D.: The Use of ACTH in Poliomyelitis, in Proceedings of the First Clinical ACTH Conference, edited by J. R. Mote, Philadelphia, The Blakiston Company, 1950, p. 522.

8. Loosli, C. G.; Hule, R. B.; Berlin, B. S., and Alexander, E. R.: The Influence of ACTH on the Course of Experimental Influenza Virus Type H Infections, Proc. Central Soc. Clin. Res. **23**:64, 1950.

evidence to indicate that this drug exerts any bactericidal or virucidal action. It is possible that the increased psychic stimulation, manifested by a remarkable feeling of well-being and alertness, and in some cases by euphoria, is the chief mechanism whereby corticotropin therapy brought about the change in these patients. Uncontrollable appetite was noted in each case, and with it a corresponding increased dietary intake. The value of high caloric intake, chiefly of carbohydrate and protein, in acute and chronic liver disease has been established by previous clinical investigators. It should be noted that all our patients maintained a fair oral intake of foods, yet the hepatitis progressed at a lively rate. It is interesting to note that in Case 2 the patient had taken a minimum of 2,400 calories a day even during the severest phase of her illness. One questions whether adequate dietary intake alone can control all cases of acute progressive hepatitis. It is noteworthy that the institution of corticotropin therapy seemed to change the course of the disease for the better in all cases. It is possible that some direct physiologic change may have occurred. The exact nature of this change, namely, of an agent blocking or modifying the effect of an infectious agent on the host cell, has not as yet been elucidated for corticotropin or for cortisone but is subject to much theoretical discussion. Possibly, suppression of antibody formation [9] by corticotropin or cortisone may account for the paradox of fall in the temperature and increase in the sense of well-being, along with completely unrestrained growth of bacterial and viral agents in the tissues of both patients and laboratory animals.

It is possible that some readjustment of the carbohydrate and protein metabolism is the means by which these compounds exert their action. Recent experiments on dietary necrotic liver degeneration in rats [10] indicate that lack of glyconeogenesis is one of the essential factors. Corticotropin and cortisone are known to be powerful stimulating agents of glycogen formation in the liver. It has been demonstrated that stress leads to an increase in the elaboration and consumption of adrenal steroids.[11] Webster [4] feels that the use of adrenal cortex extract in treatment of his series of patients augmented the needed steroids during the acute phase of hepatitis and thus maintained a balance in the body's homeostatic mechanism. In this regard, Schwarz [10] has recently demonstrated that administration of cortisone acetate, in daily doses of 1 mg. per 100 gm. of body weight, has delaying action on the development of liver degeneration in rats fed on 30% yeast diet.

We are aware of the hazards of corticotropin therapy in liver disease, namely, increased fluid retention, increased coagulability of the blood, and the possible development of portal vein thrombosis.[12] The occurrence of severe or even fatal esophageal hemorrhage has recently been reported in a patient with chronic liver disease, receiving doses of corticotropin of less than 50 mg. daily.[12] All these

9. Germuth, F. G., Jr., and Ottinger, B.: Effect of 17-Hydroxy-11-Dehydrocorticosterone (Compound E) and of ACTH in Arthus Reaction and Antibody Formation in the Rabbit, Proc. Soc. Exper. Biol. & Med. **74**:815 (Aug.) 1950.

10. Schwarz, K.: Inhibitory Effects of Cortisone on Dietary Necrotic Liver Degeneration in the Rat, Science **113**:485 (April 27) 1951.

11. Sayers, G., and Sayers, M. A.: Regulation of Pituitary Adrenocorticotrophic Activity During Response of Rat in Acute Stress, Endocrinology **40**:265 (April) 1947.

12. Bongiovanni, A. M., and Eisenmenger, W. J.: Adrenal Cortical Metabolism in Chronic Liver Disease, J. Clin. Endocrinol. **11**:152 (Feb.) 1951.

complications, however, have occurred in patients with chronic liver disease. Experimentally, Rich [13] has demonstrated deposition of large amounts of fat in the livers of rabbits treated with cortisone in a dosage of 7.5 mg. per day, intramuscularly. Corticotropin produced some fat deposition but considerably less than cortisone. The difference between these two compounds may simply be one of dosage. Further, this effect may be a species-specific one.

Although corticotropin has apparently exerted a profound effect in halting the rapid progress of acute homologous serum hepatitis in these four cases, one must not conclude that it alters the basic disease mechanism. As a matter of fact, the condition of one of our patients has gone on to a typical phase of chronic hepatitis.

SUMMARY AND CONCLUSIONS

Four patients with acute homologous serum hepatitis were treated with either corticotropin or cortisone. Defervescence and symptomatic relief occurred promptly in each case. In two instances, there was clinical relapse following discontinuation of therapy with the steroid hormone, but on reinstitution of the medication there was a rapid remission.

The probable mechanisms whereby corticotropin and cortisone exert their effect in these cases are discussed.

Dr. I. Rossman permitted publication of Case 4.

13. Rich, A. R.; Cochran, T. H., and McGoon, D. C.: Marked Lipemia Resulting from the Administration of Cortisone, Bull. Johns Hopkins Hosp. **88**:101 (Jan.) 1951.

THROMBOEMBOLIC PULMONARY VASCULAR SCLEROSIS

Report of a Case Following Pregnancy and of a Case Associated with Cryoglobulinemia

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THE COMBINATION of widespread sclerosis of the pulmonary arterial tree and cardiopulmonary failure has been the source of repeated discussions during the past 60 years.[1] Brenner's extensive reviews [1e,f] have served to emphasize the

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1. (*a*) Romberg, E.: Ueber Sklerose der Lungenarterie, Deutsches Arch. klin. Med. **48**:197-206, 1891. (*b*) Sansom, A. E.: Diseases of the Pulmonary Artery, in Twentieth Century Practice of Medicine, New York, William Wood & Company, 1896, pp. 522-525. (*c*) Posselt, A.: Die Erkrankungen der Lungenschlagader, Ergebn. allg. Path. u. path. Anat. **13**:298-526, 1909. (*d*) Escudero, P.: Les cardiaques noirs et la maladie de Ayerza, Arch. mal. cœur **19**:439-445, 1926. Arrillaga, F. C.: (*e*) Cardiacos negros, Buenos Aires, 1913; (*f*) Sclérose de l'artère pulmonaire secondaire à certains états pulmonaires chroniques, Arch. mal. cœur **6**:518-529, 1913. (*g*) Arrillaga, F. C., and Elizalde, P. I.: Caractères histopathologiques de la maladie de Ayerza, Compt. rend. Soc. biol. **84**:161, 1921. (*h*) Mönckeberg, J. G.: Ueber die genuine Arteriosklerose der Lungenarterie, Deutsche med. Wchnschr. **33**:1243-1246, 1907. (*i*) Rössle, R.: Ueber Hypertrophie und Organkorrelation, München. med. Wchnschr. **55**:377-381, 1908. (*j*) Sanders, W. E.: Primary Pulmonary Arteriosclerosis with Hypertrophy of the Right Ventricle, Arch. Int. Med. **3**:257-262 (April) 1909. (*k*) Schütte, H.: Rechtsseitige Herzhypertrophie hervorgerufen durch eine entzündliche Veränderung der kleinen Lungenarterien, Centralbl. allg. Path. u. path. Anat. **25**:483-485, 1914. (*l*) Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufs, Wiesbaden, J. F. Bergmann, 1915. (*m*) Hart, C.: Ueber die isolierte Sklerose der Pulmonalarterie, Berl. klin. Wchnschr. **53**:304-306, 1916. (*n*) Krutzsch, G.: Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, Frankfurt. Ztschr. Path. **23**:247-271, 1920. (*o*) Eppinger, H., and Wagner, R.: Zur Pathologie der Lunge, Wien. Arch. inn. Med. **156**:83-146, 1920. (*p*) Tschistowitsch, T.: Thrombo-endoartérite pulmonaire chronique, Compt. rend. Soc. biol. **89**:627, 1923. (*q*) Goedel, A.: Zur Kenntnis der Hypertrophie des rechten Herzens und schwerer Kreislaufstörung infolge Verödung der Lungenschlagaderperipherie, Arch. path. Anat. **277**:507-521, 1930. (*r*) Kuntschik, R.: Zur Kenntnis der sogenannten primären Pulmonalsklerose, Ztschr. Kreislaufforsch. **23**:183-198, 1931. (*s*) MacCallum, W. G.: Obliterative Pulmonary Arteriolosclerosis, Bull. Johns Hopkins Hosp. **49**:37-48, 1931. (*t*) Ulrich, H. L.: The Clinical Diagnosis of Pulmonary Arteriosclerosis, Ann. Int. Med. **6**:632-644, 1932. (*u*) Killingsworth, W. P., and Gibson, S.: Primary Proliferative Pulmonary Arteriolar Sclerosis, Am. J. Dis. Child. **57**:1099-1109 (May) 1939. (*v*) Brill, I. C., and Krygier, J. J.: Primary Pulmonary Vascular Sclerosis, Arch. Int. Med. **68**:560-577 (Sept.) 1941. (*w*) Cross, K. R., and Kobayashi, C. K.: Primary Pulmonary Vascular Sclerosis, Am. J. Clin. Path. **17**:155-162, 1947. (*x*) Warthin, H. S.: Syphilis of the Pulmonary Artery: Syphilitic Aneurysm of the Left Upper Division: Demonstration of

(Footnote continued on next page)

complexities of this combination. Particularly enigmatic has been the pathogenesis of primary pulmonary vascular sclerosis. In the present communication we wish to record two additional cases displaying widespread thrombotic or embolic masses within small pulmonary arteries and pulmonary vascular sclerosis of a sufficient magnitude to effect cardiopulmonary failure (Ayerza's syndrome). Human cases of this type, which have been periodically recorded, merely indicate the association of thrombi or emboli and the vascular lesions. The experimental intravenous injection of small embolic masses, on the other hand, by evoking a similar vascular sclerosis indicates a cause and effect in this relationship. In a separate report [2] the

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Spirochaeta Pallida in the Wall of the Artery and the Aneurysmal Sac, Am. J. Syphilis **1**:693, 1917. (*y*) Rogers, L.: Extensive Atheroma and Dilatation of the Pulmonary Arteries, Without Marked Valvular Lesions, as a Not Very Rare Cause of Fatal Cardiac Disease in Bengal, Quart. J. Med. **2**:1-18, 1908. (*z*) Cheney, G.: Ayerza's Disease: Report of 2 Cases, Am. J. M. Sc. **174**:34-45, 1927. (*a'*) Veale, P. J., and Coombs, C.: Cardiac Failure in a Child, Aged 6 Years, Associated with Atheroma of the Pulmonary Artery and Extreme Dilatation of the Right Ventricle, Brit. J. Child. Dis. **12**:72-77, 1915. (*b'*) Bacon, C. M., and Apfelbach, C. W.: Primary Sclerosis of the Pulmonary Artery and Its Branches, Arch. Path. & Lab. Med. **3**:801-815 (May) 1927. (*c'*) Konstam, G. L. S., and Turnbull, H. M.: Syphilis of the Lung with Pulmonary Arteritis (Ayerza's Disease), Lancet **2**:756-761, 1920. (*d'*) Hare, D. C., and Ross, J. M.: Syphilitic Disease of the Pulmonary Arteries, with Account of Case, ibid. **2**:806-812, 1929. (*e'*) Brenner, O.: Pathology of the Vessels of the Pulmonary Circulation, Arch. Int. Med. **56**:976-1014 (Oct.); 1189-1241 (Dec.) 1935. (*f'*) Parker, F., Jr., and Weiss, S.: The Nature and Significance of the Structural Changes in the Lungs in Mitral Stenosis, Am. J. Path. **12**:573-598, 1936. (*g'*) Larrabee, W. F.; Parker, R. L., and Edwards, J. E.: Pathology of Intrapulmonary Arteries and Arterioles in Mitral Stenosis, Proc. Staff Meet., Mayo Clin. **24**:316-326, 1949. (*h'*) Friedberg, C. K.: Diseases of the Heart, Philadelphia, W. B. Saunders Company, 1949. (*i'*) Greenspan, E. B.: Carcinomatous Endarteritis of Pulmonary Vessels Resulting in Failure of the Right Ventricle, Arch. Int. Med. **54**:625-644 (Oct.) 1934. (*j'*) Brill, I. C., and Robertson, T. D.: Subacute Cor Pulmonale, ibid. **60**:1043-1057 (Dec.) 1937. (*k'*) Morgan, A. D.: The Pathology of Subacute Cor Pulmonale in Diffuse Carcinomatosis of the Lungs, J. Path. & Bact. **61**:75-84, 1949. (*l'*) Welch, K. J., and Kinney, T. D.: The Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defects on the Development of Pulmonary Vascular Lesions, Am. J. Path. **24**:729-761, 1948. (*m'*) Ljungdahl, M.: Gibt es eine chronische Embolisierung der Lungenarterienembolien? Deutsches Arch. klin. Med. **160**: 1-23, 1928. (*n'*) Frothingham, C.: A Case of Extensive Bilateral Progressive Thrombosis of the Smaller Branches of the Pulmonary Arteries, Am. J. Path. **5**:11-22, 1929. (*o'*) Castleman, B., and Bland, E. F.: Organized Emboli of the Tertiary Pulmonary Arteries, Arch. Path. **42**:581-589 (Dec.) 1946. (*p'*) Means, J. H., and Mallory, T. B.: Total Occlusion of the Right Branch of the Pulmonary Artery by an Organized Thrombus, Ann. Int. Med. **5**:417-427, 1931. (*q'*) Brenner, O.: Sclerosis of the Pulmonary Artery with Thrombosis, Lancet **1**:911-914, 1931. (*r'*) Gordon, H., and Perla, D.: Subacute Bacterial Endarteritis of Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonary Stenosis, Am. J. Dis. Child. **41**:98-109 (Jan.) 1931. (*s'*) Pirani, C. L.; Ewart, F. E., and Wilson, A. L.: Thromboendarteritis with Multiple Mycotic Aneurysms of Branches of the Pulmonary Artery, ibid. **77**:460-473 (April) 1949. (*t'*) Spencer, H.: Primary Pulmonary Hypertension and Related Vascular Changes in the Lungs, J. Path. & Bact. **62**:75-84, 1950. (*u'*) Gilmour, J. R., and Evans, W.: Primary Pulmonary Hypertension, ibid. **58**:687-697, 1946. (*v'*) Spain, D. M.: Patterns of Pulmonary Fibrosis as Related to Pulmonary Function, Ann. Int. Med. **33**:1150-1163, 1950. (*w'*) Harrison, C. V.: Experimental Pulmonary Arteriosclerosis, J. Path. & Bact. **60**:289-293, 1948. (*x'*) Karsner, H. T.; Simon, M. A., and Fujiwara, T. F.: Relation of Experimental Pulmonary Arterial Hypertension to Arteriosclerosis, Arch. Path. **31**:585-591 (May) 1941.

2. Muirhead, E. E., and Montgomery, P. O'B.: Thromboembolic Pulmonary Arteritis and Vascular Sclerosis: Its Experimental Production in Rabbits by Means of Intravenously Injected Human Amniotic Fluid and Autogenous Blood Clots, A. M. A. Arch. Path. **52**:505-517 (Dec.) 1951.

experimental production of pulmonary vascular sclerosis in the rabbit by means of embolic masses is being presented. It appears that in both the human and the experimental observations the occlusive masses become masked by the sclerosis, thus eventuating in a morphologic picture similar to that of primary vascular sclerosis without the evident thrombi or emboli.

REVIEW OF LITERATURE

At the turn of the century, attention was focused on the combination of pulmonary vascular sclerosis and cardiopulmonary failure as a consequence of the discussions by Ayerza and his followers,[1d-g] the report of Mönckeberg,[1h] and a review of the diseases of the pulmonary arteries by Posselt.[1c] Ayerza, in 1901, in unpublished discussions, emphasized the condition of *cardiacos negros*, a topic that was the source of several discussions by his associates, especially Escudero [1d] and Arrillaga.[1e-g] Mönckeberg [1h] introduced the term primary pulmonary vascular sclerosis. Posselt's review emphasized primary pulmonary vascular sclerosis and, in addition, recorded 18 reports of pulmonary thrombosis with endarteritis.

Romberg,[1a] in 1891, described the case of a young man revealing extensive pulmonary vascular sclerosis, hypertrophy of the right ventricle, and a clinical state including dyspnea and cyanosis of several months' duration. Sansom,[1b] in 1896, reviewed this subject and pointed out the influence of septic endocarditis in the genesis of pulmonary arterial sclerosis. Escudero, in 1911, considered the sclerosis of the pulmonary vasculature in *cardiacos negros* as a complication of bronchial syphilis. In 1913 Arrillaga favored the view that emphysema of varied backgrounds formed the basis for the vascular sclerosis, which in turn initiated the marked hypertrophy of the right side of the heart, hypertrophy and dilatation of the pulmonary artery visible on roentgen examination, cyanosis, polycythemia, dyspnea, hemoptysis, vertigo, and drowsiness. Subsequently, Arrillaga supported the syphilitic causation of *cardiacos negros*, thus relegating the cardiopulmonary failure to a secondary position. The concept of pulmonary syphilitic endarteritis was additionally supported by the observations of Warthin [1x] and others.[1y,z] During this earlier period, however, the fact that a similar pulmonary lesion and symptom complex could occur in the absence of demonstrable syphilis was apparent in other reports.[1a',b'] Although the syphilitic origin of pulmonary arterial sclerosis has been supported even recently by Konstam [1c'] and Hare and Ross,[1d'] it has become apparent in a series of additional reports, as discussed by Brenner,[1e'] that pulmonary vascular sclerosis has a heterogeneous background and "that primary sclerosis is not a pathologic entity but that several different conditions are included under the same name." [1e']

Pulmonary vascular sclerosis, mainly of the endarteritic type, is usually a complication of a number of diseases associated with pulmonary hypertension.[1f'-l'] Thus, it is observed in conjunction with mitral stenosis, pulmonary fibrosis, interstitial pneumonitis, lymphangitic carcinomatosis, and a large patent ductus arteriosus. In this secondary type of pulmonary endarteritis the primary disease is foremost, and, accordingly, the endarteritis may not be entirely appreciated until the postmortem examination.

Less commonly, pulmonary vascular sclerosis is primary. Brenner [1e'] considered a case acceptable as primary when widespread pulmonary vascular sclerosis occurred in the absence of a demonstrable chronic cardiac or pulmonary disease and in the

presence of marked hypertrophy of the right ventricle and a symptom complex including cyanosis, frequently polycythemia, right heart failure, and minimal dyspnea.

Brill and Krygier,[1v] in 1941, reviewed the literature dealing with primary pulmonary vascular sclerosis. According to Brenner's criteria,[1e'] these authors accepted only 20 cases as authentic, including a case they reported. In five (25%) of these cases (those of Tschistowitsch,[1p] Goedel,[1q] Kuntschik,[1r] MacCallum,[1s] and Brill and Krygier [1v]) small thrombi of various ages were described in small pulmonary arteries. In an additional case, that of Hart,[1m] a thrombus was present in one of the larger pulmonary arteries. Brill and Krygier accepted MacCallum's explanation that the thrombosis was secondary to the sclerosis. The minute thrombi, however, were so striking to Tschistowitsch that this author labeled his case one of chronic pulmonary thromboendarteritis.[1p]

Congenital inferiority of the pulmonary vessels, an additional earlier concept of the pathogenesis of primary pulmonary vascular sclerosis, was rejected by Brenner,[1e'] who could not disregard entirely the possible role of either infection or widespread pulmonary embolism or thrombosis in the genesis of some of these cases. Although pulmonary thrombosis or embolism was associated with vascular sclerosis in the several reports alluded to previously, in the cases described by Ljungdahl,[1m'] Eppinger and Wagner,[1o] and Frothingham [1n'] a more clear-cut relationship between widespread thrombosis of small branches of the pulmonary arteries, advanced pulmonary endarteritis, and cardiopulmonary failure was noted. The case of Castleman and Bland [1o'] had extensive organized emboli of the tertiary pulmonary arteries. Other reports [1p'-u'] have mentioned, with varying emphasis, the concomitant presence of small emboli or thrombi and endarteritis on the microscopic examination of the lungs. Spain [1v'] related a case of pulmonary vascular fibrosis secondary to pulmonary emboli of a foreign-body type.

Impressed by the occurrence of multiple thrombi and pulmonary vascular sclerosis in one of his cases, Harrison [1w'] produced a transient pulmonary endarteritis in rabbits by means of intravenously injected emboli in the form of human fibrinous blood clots. This author [1w'] reviewed Duguid's concept of thrombosis as the basis for certain forms of arteriosclerosis. Karsner and co-workers [1x'] demonstrated earlier the development of pulmonary vascular sclerosis by the experimental injection of Lycopodium spores.

It appears evident from the literature that a relationship between widespread embolism or thrombosis of small pulmonary arteries and pulmonary vascular sclerosis (or endarteritis) has been repeatedly considered in the past. Moreover, the degree of pulmonary endarteritis has been of a sufficient magnitude to effect cardiopulmonary failure. It remains to be established what percentage of so-called primary pulmonary vascular sclerosis can be explained by this mechanism. In view of the rarity of primary pulmonary vascular sclerosis, the opportunities to demonstrate a clear-cut relationship between it and the presence of thrombotic and/or embolic masses in pulmonary vessels have not been many. It is for this and other reasons cited below that we believe the two cases herein reported are of interest.

Both cases demonstrate the combination of cardiopulmonary failure, widespread pulmonary vascular sclerosis, and widespread embolic or thrombotic masses in the smaller branches of the pulmonary arteries. The first patient's clinical course began shortly after the delivery of her second child; the lungs contained occlusive masses of a thromboembolic type within the small pulmonary arteries. In the second patient

unexplained right heart failure occurred in the presence of marked hyperglobulinemia and cryoglobulinemia.[3] The occlusive masses within the finer pulmonary vessels were interesting, since they consisted of protein-like precipitate. The possibility of a spontaneous precipitation of the unstable globulin within the pulmonary vessels requires consideration.

These observations led to an additional attempt to produce experimentally pulmonary endarteritis in the rabbit by the repeated intravenous injection of small embolic masses, according to a modification of Harrison's technic. As reported separately,[2] in those animals surviving repeated injections, this technic was successful.

REPORT OF CASES

CASE 1.—*History.*—A 27-year-old white housewife was admitted to the hospital with the chief complaint of dyspnea. Nine months before the patient had delivered her second baby by breech presentation. During the latter weeks of pregnancy she had experienced some shortness of breath but, according to her, no more than she had had during her first pregnancy. The baby was delivered in a local hospital, and review of the clinical record revealed no abnormal symptoms during parturition or during the postpartum period. She was discharged in the usual time in apparent good health. In the succeeding two weeks voice change was noted, and she consulted an otolaryngologist, who observed vocal cord paralysis on the left. The patient was referred to an internist, who noted no abnormal findings in the lungs, heart, or mediastinum. A posteroanterior roentgenogram of the chest at that time revealed no infiltration of the lung fields and a normal heart shadow, with possible prominence of the pulmonary artery segment. There was no evidence of an upper mediastinal mass. The presence of left vocal cord paralysis was confirmed by a second laryngologist.

No other symptoms were noted by the patient at that time, although the husband stated that while walking with the patient he noted that she was forced to stop periodically because of shortness of breath. Six months after delivery, on attending football games, the patient had to stop to get her breath while walking up the ramps.

Two months later (eight months after the delivery) increasing dyspnea, mild cyanosis, and nausea and vomiting appeared. During this period she was observed by a neurosurgeon because of left hemiplegia. This lasted 12 to 18 hours and cleared spontaneously. The patient was admitted to the hospital shortly thereafter. For two weeks the dyspnea had become more pronounced. In addition, she had experienced substernal pressure and pain extending to both shoulders. Earaches and headaches became severe.

Physical examination revealed a white woman, propped in bed, markedly dyspneic, and revealing mild cyanosis. The temperature was 98 F., the pulse rate 100, the respiratory rate 25, and the blood pressure 150/100 mm. Hg. The neck veins were overly distended, and the liver was markedly enlarged. During the following two months systolic murmurs appeared and disappeared over the lower portion of the heart but were not heard at the base. Dyspnea remained great, and an oxygen mask was kept on almost continuously. At all times rales were absent and roentgenographic study of the chest showed no abnormality in the lung fields.

Three days before death an observer noted the following: Cyanosis was evident even when the B-L-B inhalation mask was attached and oxygen ran at 10 liters per minute. The neck veins were greatly distended, and a ventricular type of pulsation was noted. Positive pulsations were noted in a vein on the volar aspect of the right wrist. The liver extended down to the level of the umbilicus, but no pulsations were noted. Auscultation of the lung fields revealed no positive findings. No murmurs were heard at the base of the heart. At the mitral area a systolic murmur was heard which was diminished in intensity in the postinspiratory apneic phase. At the lower border of the sternum to the left a systolic murmur was heard which was intensified by the

3. Lerner, A. B., and Watson, C. J.: Studies of Cryoglobulins: Unusual Purpura Associated with Presence of High Concentration of Cryoglobulin (Cold Precipitable Serum Globulin), Am. J. M. Sc. **214**:410-415; 416-421, 1947. Barr, D. P.; Reoder, G. G., and Wheeler, C. H.: Cryoglobulinemia: I. Report of 2 Cases with Discussion of Clinical Manifestations, Incidence and Significance, Ann. Int. Med. **32**:6-29, 1950.

postinspiratory apneic phase. Venous pressure was 200 mm. of water; the circulation time, arm to lung, was 13 seconds, and arm to tongue, 30 seconds. No edema of the extremities was noted. The neurologic examination disclosed no abnormalities.

Laboratory Data (obtained during the first week of hospitalization).—The hemoglobin concentration was 18.65 gm. per 100 cc. Red blood cells were 6,450,000, and white blood cells, 11,200, with a differential count of 7 band cells, 67 segmented cells, 17 lymphocytes, 8 monocytes, and 1 eosinophil. The Kline, Kahn, Mazzini, and Wassermann reactions of the blood were negative. Many urinalyses revealed similar findings: The specific gravity was 1.025, with an acid reaction. The amount of albumin present varied from a trace to 500 mg. per 100 cc. Reactions for sugar, acetone, and diacetic acid were negative. The sediment showed a rare red blood cell, few to frequent white blood cells, and many epithelial cells. The phenolsulfonphthalein test showed 43% excretion in one hour (32% in 15 minutes). Plasma protein was 6.1 gm., with 3.7 gm. of albumin and 2.4 gm. of globulin, per 100 cc. The dextrose tolerance test showed a fasting level of 98 mg. per 100 cc. of blood. At one hour the level was 110 mg., at two hours, 119 mg., and at three hours 129 mg. Blood cholesterol was 180 mg. per 100 cc.; plasma chloride was 100 mEq. per liter, and blood urea was 47 mg. The spinal fluid was normal. Blood culture yielded no growth. Other examinations revealed 4.6% reticulocytes, a thrombocyte count of 156,000, and a sedimentation rate of 1 mm. in 60 minutes.

A roentgenogram taken on admission was interpreted as showing the following: (1) slight cardiac enlargement, (2) slight disproportionate right ventricular enlargement, (3) the possibility of isolated pulmonary stenosis, (4) the possibility of interatrial septal defect, and (5) no evidence of an abnormality involving the skull or its contents. Two electrocardiographic tracings were interpreted similarly: Each was "an abnormal tracing with sinus tachycardia, right axis deviation, ST-T changes, and right ventricular hypertrophy pattern." An intake-output chart revealed a satisfactory fluid balance.

The patient was digitalized and given mercurial diuretics periodically, sedatives, 1 liter of dextrose in water intravenously daily as indicated, vitamins, and continuous oxygen. Little food or fluids were taken by mouth. The temperature remained between 97 and 98 F. and the pulse rate between 70 and 90, and dyspnea persisted. The course was downhill. The blood pressure dropped to 100/80 during the first week and to 90/50 during the second week, remaining near this level until terminally. She remained apprehensive. Death occurred approximately nine months after the onset of dyspnea on exertion (the 50th hospital day).

Synopsis of Autopsy Observations (two hours after death).—Gross Observations: The peritoneal cavity contained 800 cc. of clear yellow fluid. The liver was 4 cm. below the costal margin in the midclavicular line. The right leaf of the diaphragm was at the level of the sixth rib and the left leaf at the sixth intercostal space. The pleural spaces contained no fluid and no adhesions. The lungs appeared collapsed within their spaces. The pericardium had 75 cc. of clear fluid. The right auricle and right ventricle were obviously dilated; scattered petechiae were seen over the epicardium.

The heart weighed 350 gm. The valves were unaltered. The right ventricle averaged 1.8 cm. in thickness and equaled the thickness of the left ventricle, which also averaged 1.8 cm. The myocardium was everywhere of normal appearance. The coronary arteries appeared unaltered. The weight of the right lung was 225 gm.; that of the left lung, 210 gm. The lungs were everywhere crepitant and of normal consistency and appearance. The pleurae were smooth throughout. The bronchi had a small amount of hemorrhagic fluid. An unattached embolus was present at the bifurcation of the artery to the basal portion of the right lower lobe. The liver weighed 1,560 gm. The spleen weighed 210 gm. The gastrointestinal tract, gall bladder, and pancreas were normal in appearance. The right kidney weighed 160 gm., the left, 150 gm. At the lower pole of the left kidney there was a small pale infarct. The adrenal glands were normal. The veins of the right broad ligament were filled with partly adherent thrombi. A small pedunculated fibroid was attached to the fundus of the uterus. Permission for examination of the central nervous system was not granted.

Microscopic Observations: The myocardium was normal. The lungs revealed alveolar spaces that were mostly empty. The small arteries in all sections from all lobes showed marked changes. A rare vessel was distended with a recent thrombus or embolus (Fig. 1*A*). In some small arteries the thrombotic mass was partly invaded by cells resembling the endothelium of the vessel

(Fig. 2*B*). An unusual finding was that of a small artery occluded by a thrombotic or embolic mass and showing partial necrosis of its media (Fig. 2*A*). The smooth muscle fibers of the media were partly changed into a reddish granular structure devoid of nuclei. Many vessels showed

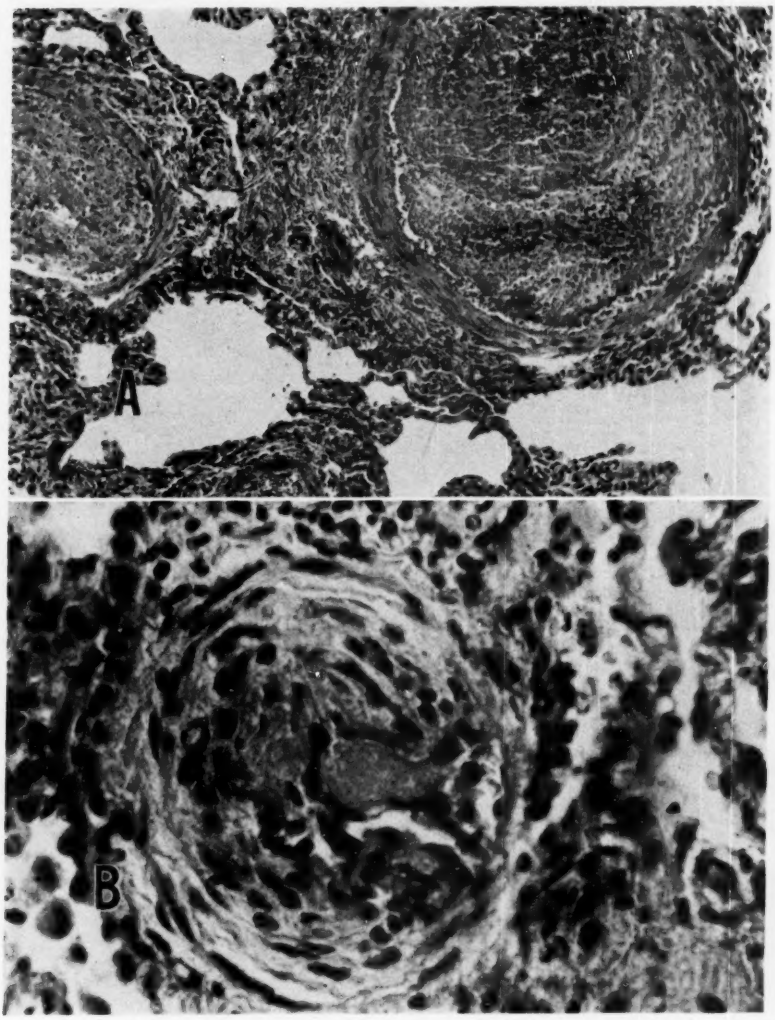

Fig. 1 (Case 1).—*A*, small arteries distended with fresh thromboembolic masses. Scattered inflammatory cells are present in adventitia. × 300. *B*, small artery containing remnant of thromboembolic mass and displaying intimal and medial fibrosis. The wall is thickened and the small lumen is eccentric. × 420.

a combination of a remnant of an occlusive mass and marked thickening of the wall (Figs. 1*B* and 4*A*). The thickening was usually eccentric and displaced the lumen to one side. It apparently

involved the subendothelial connective tissue. Many vessels revealed a marked thickening of the wall due to a hypercellularity associated with a marked narrowing of the lumen bordering on obliteration (Fig. 3*A*). Masson's trichrome stain indicated the connective tissue composition of these hypercellular and thickened vessels. In several microscopic lung fields only the latter type

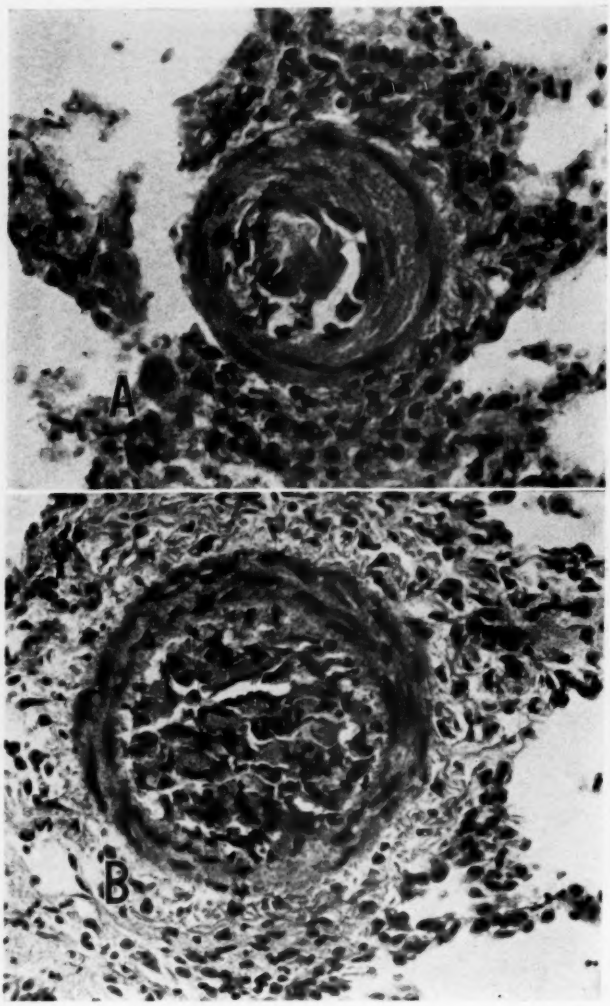

Fig. 2 (Case 1).—*A*, small artery containing a fresh thromboembolic mass showing necrosis of the media. × 420. *B*, lumen of this small artery is occluded by a mass which has been invaded by endothelial cells in an irregular manner. × 320.

of blood vessels was seen, and here the association with occlusive masses within the lumina could not be identified. Another type of change, involving larger arteries, was characterized by the subendothelial accumulation of a loose and delicate type of connective tissue (Fig. 3*B*). This

Fig. 3 (Case 1).—*A*, small artery with thickened wall and obliterated lumen. Cellular tissue composing the wall has tinctorial characteristics of connective tissue. There is pneumonitis in the vicinity. × 300. *B*, artery with intact internal elastic lamina and marked thickening of intima due to accumulation of a loose connective tissue. Elastic stain; × 300.

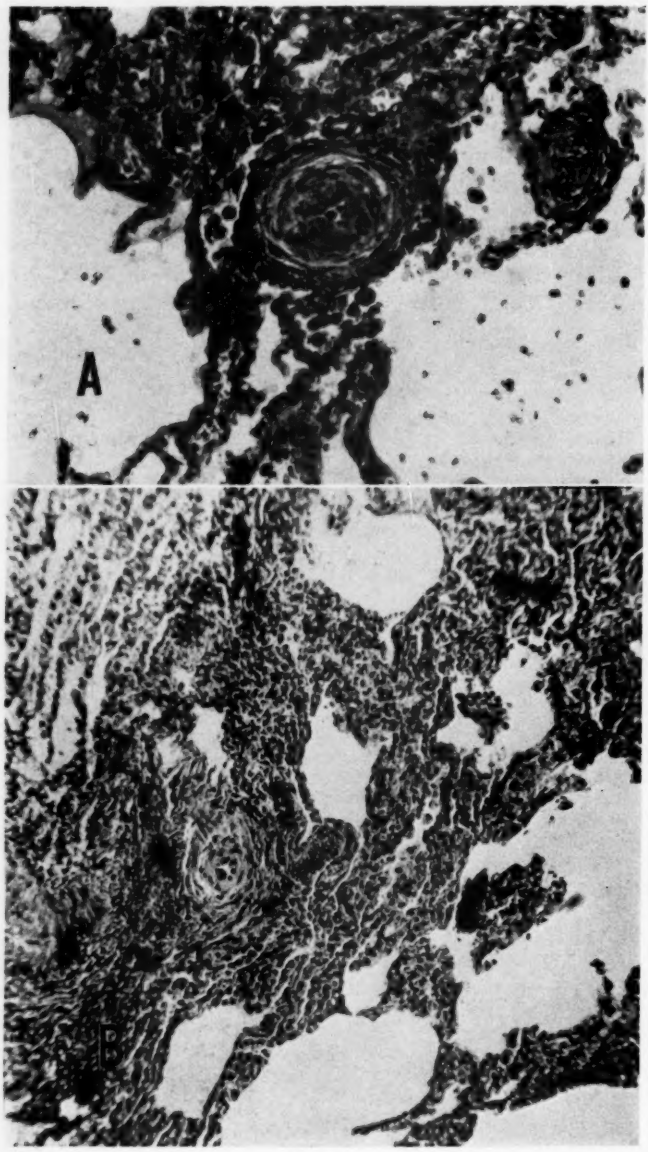

Fig. 4 (Case 1).—*A*, small artery displaying remnant of occlusive mass, eccentric lumen, and eccentric fibrosis of its wall. Trichrome stain; × 210. *B*, thickened artery in center of area of chronic pneumonitis. × 120.

connective tissue interposed between the endothelium and the internal elastic lamina, causing a marked narrowing of the vascular lumen. The obstruction and thickening of the blood vessels were noted in all lung sections and appeared to be widespread. There were focal areas in which the alveolar walls were thickened by fibrous tissue and the infiltration of lymphocytes and macrophages (Fig. 4*B*). These focal zones of pneumonitis occurred particularly near vessels containing thrombi. Occasionally, the adventitia of occluded arteries also contained lymphocytes and a few neutrophilic leucocytes (Figs. 2*A* and 1*B*). On a few occasions the alveoli near the areas of pneumonitis contained lipid-laden macrophages.

The liver showed passive hyperemia with centrolobular atrophy and necrosis. No other significant findings were noted microscopically.

Diagnoses.—Anatomic diagnoses were as follows: (1) widespread pulmonary vascular sclerosis (endarteritis); (2) multiple organizing pulmonary emboli or thrombi; (3) recent pulmonary embolism, right lower lobe; (4) chronic focal pneumonitis; (5) marked hypertrophy and dilatation, right ventricle; (6) thrombosis, vein of right broad ligament; (7) passive visceral hyperemia; (8) central atrophy and necrosis of liver; (9) ascites; (10) old, small infarct, left kidney.

CASE 2.—*History.*—A 48-year-old Negro woman was admitted with the following chief complaints: (1) headaches for five months, (2) bouts of vomiting for five months, (3) increasing drowsiness and irrational talk for two weeks, and (4) severe headaches for two days. This was the second hospital admission of this patient within six months. She was confused and drowsy on admission, and the history was obtained from her and from members of the family. Six months prior to this admission, she was in this hospital, at which time hysterectomy and bilateral salpingo-oophorectomy were performed. The uterus revealed leiomyomata, and the uterine tubes, healed salpingitis. She received 7 pt. (3,311 cc.) of blood at that time; otherwise the operation was uncomplicated. The reactions to serologic tests for syphilis were recorded as positive. The patient dated all her illness to the first period of hospitalization. After the discharge she experienced frequent headaches, which were throbbing in nature but ill defined in location. She vomited periodically during this interval, and on one occasion she was admitted to the emergency room for treatment of obstipation but recovered after an enema. The frontal headaches became severe three days before admission. The family had noted increasing drowsiness, culminating in almost continuous sleep for two days. The past history revealed that she had fallen once during the past year, striking her head, but consciousness was not lost. Otherwise, the hysterectomy was the main event. The reviews of systems indicated that she had had poor hearing and vision for 8 to 10 years. She had had no headaches prior to the present illness. The patient would become short of breath after walking five blocks. There was no knowledge of hypertension in the past. Cough, chest pain, and orthopnea were denied. Since the operation swelling of the right ankle occasionally developed which subsided spontaneously. She had been treated for syphilis 11 years before, after the birth of a stillborn child. After the positive serologic reactions were discovered six months ago, she received a course of 13,600,000 units of penicillin. Nocturia, four to five times, had been present since the operation. Attacks of dysuria had taken place when she was a child. Menarche occurred at the age of 16. She had had two stillbirths. There were no other abnormalities until last year, when the uterine bleeding, which was associated with a severe anemia (hemoglobin concentration, 4 gm. per 100 cc.), occurred.

Physical examination revealed a poorly nourished Negro woman, lying quietly and answering questions slowly. Her hearing was poor, and, unless stimulated by questions, she dropped off to sleep. The temperature was 98 F., the pulse rate, 80, the respiratory rate 20, and the blood pressure 200/140 (left arm) and 180/130 (right arm). The skin was warm and smooth throughout. There was a slight decrease of skin turgor. The right pupil measured 6 mm. and the left 3 mm. in diameter. The left pupil reacted slightly to light, but the right did not. The extraocular muscles were intact. Funduscopic examination revealed normal disks, an arterial-venous ratio of 1:3, slight arteriovenous nicking, and no hemorrhage or exudate. The mouth was edentulous. The neck was supple, and there were no cervical masses. The chest was thin, and the lung fields were clear. The point of maximal impulse was not palpable, but the left heart border was considered to be inside the midclavicular line. There were no murmurs. The rhythm was regular. There was marked diastasis recti; no abnormal masses were felt. A midline suprapubic scar was well healed. There was slight generalized lymphadenopathy. The extremities were normal. The knee jerks were graded as 3+; otherwise the neurological examination gave normal results.

Laboratory Data (obtained shortly after admission).—Red blood cells numbered 5,500,000. The hemoglobin concentration was 13.3 gm. per 100 cc. The white blood cell count was 4,700, with a differential count of 60 segmented forms, 5 band forms, 1 eosinophil, and 34 lymphocytes. A sickle-cell preparation showed no sickling. Urea was 180 mg., and total serum protein, 13.2 gm., with 3.3 gm. of albumin and 9.9 gm. of globulin, per 100 cc. Plasma chloride was 85 mEq., and bicarbonate 30 mEq. per liter. Serum calcium measured 9.4 mg. and serum phosphorus 5 mg. per 100 cc. Studies of the spinal fluid disclosed 194 mg. of protein and 55 mg. of sugar per 100 cc., with a negative Wassermann reaction and a colloidal gold curve of 55555420000. On urinalysis the specific gravity was 1.008. The urine was alkaline, with a 1+ reaction for albumin and negative reactions for sugar and acetone. The sediment showed a few white blood cells and rare hyaline casts. The phenolsulfonphthalein test revealed 4% excretion in 45 minutes. Three bone marrow examinations were performed within two weeks, and the results were interpreted as follows: 1. Marrow from the sternum showed the myeloid-erythroid ratio to be normal, with 7.5% plasma cells, mostly of well-differentiated type. 2. In marrow from the left ilium the myeloid-erythroid ratio was 9:1, with 8% plasma cells suggestive of myeloma. 3. Marrow from a spinous process had a normal myeloid-erythroid ratio and 14.5% plasma cells, as well as frequent undifferentiated plasma cells considered to be myeloma cells. Rouleaux formation was marked. Bence Jones protein was not detected in the urine. The serum gave a strongly positive reaction for cryoglobulins. A quantitative determination of this cold-precipitable globulin was not conducted, but, when plasma or serum was left overnight in the icebox, a prominent flocculation occurred which disappeared on warming to 37 C. Electrophoretic studies of this patient's serum revealed a decrease in the albumin peak, with a prominent beta and gamma globulin peak and no intermediate globulin. Multiple roentgenograms of the skeleton did not reveal destructive lesions.

Course in Hospital.—The patient was placed on a hypertensive low-sodium diet and was given 3,000 cc. of fluid daily. On this regimen the blood urea receded to 30 mg. per 100 cc. within five days; at the same time the blood pressure dropped to 136/70 mm. Hg. Culture of the urine yielded a heavy growth of Escherichia coli. She was given streptomycin, 0.5 gm. two times daily for eight days. The urine culture became negative for the pathogen, but the fever persisted. The plasma chloride remained near 82 mEq. per liter, and 6 gm. of sodium chloride daily was added to her diet. A histamine test for pheochromocytoma gave a negative reaction. A test for Raynaud's disease (hand in ice water 10 minutes) revealed a reactive flush in 5 minutes, the hand remaining cold for 20 minutes. The 24-hour urinary chloride excretion varied between 32 and 60 mEq. per liter on five occasions, and the intake of sodium chloride was lowered to 3 gm. daily. Throughout the remainder of the course, the patient maintained a low-grade fever (elevation in temperature to 99 to 101 F.) with an afternoon peak. The pulse rate varied between 80 and 110. The blood pressure remained about 115/70 mm. Hg. The blood urea varied between 19 and 45 mg. per 100 cc.; the plasma chlorides were elevated to 97 mEq. per liter and remained near this level. A second phenolsulfonphthalein test revealed 55% excretion in two hours. The daily urinary output varied between 800 and 2,200 cc. but was usually less than 1,000 cc. The urinary specific gravity varied between 1.010 and 1.022. Albuminuria (1 to 3+) persisted; rare hyaline casts and few white blood cells were noted. Hyperglobulinemia (7.5 to 9 gm. per 100 cc.) was demonstrated five additional times. The white blood cell count dropped to near 4,000 and remained there. The hemoglobin concentration leveled off between 10 and 11 gm. per 100 cc. Urethan was given during the fourth week without benefit. Six weeks after admission she exhibited a cough on lying down and displayed basal rales. The patient was digitalized. The cough and basal rales did not respond to digitalization. A roentgen examination of the chest at this time revealed marked enlargement of the cardiac silhouette. The vital capacity was recorded as 1,350 cc. The circulation time (dehydrocholic acid [decholin®]) was 16 seconds. Blood cultures were negative for pathogens. An electrocardiogram was interpreted as showing (1) low amplitude of the complexes in the standard leads and (2) change in the T waves compatible with acute myocardial change or digitalis effect. The patient remained febrile and chronically ill. On the 62d hospital day, it was decided that she should be discharged and followed in the outpatient clinic.

One month after leaving the hospital, the patient was readmitted for the final time. Since her discharge edema of the feet and ankles had developed. The nocturnal cough, nonproductive, persisted. On admission the temperature was 98.6 F., the pulse rate 116, the respiratory rate 118, and the blood pressure 140/110. Funduscopic examination disclosed minimal arteriovenous nick-

ing and an arterial-venous ratio of 1 : 3. Slight stiffness of the neck and venous distention were recorded. A left submaxillary lymph node 2 cm. in diameter and slight axillary lymphadenopathy were noted. The point of maximal impulse was in the sixth interspace 1 cm. left of the midclavicular line. The pulmonary second sound was louder than the aortic second sound. The rhythm was regular. Few rales were heard at the bases. The liver was palpable 4 cm. below the right costal margin. Slight pitting edema of the feet and ankles was present.

Final Laboratory Data.—The hemoglobin concentration was 14.2 gm. per 100 cc. The white blood cell count was 10,500, with a differential count of 7 band cells, 60 segmented cells, 25 lymphocytes, and 8 monocytes. Blood urea was 37 mg. and total serum protein 9.6 gm., with 6.8 gm. of globulin, per 100 cc. Plasma bicarbonate was 20 mEq. and plasma chloride 97.5 mEq. per liter. Blood creatinine measured 1.5 mg. and blood cholesterol 162 mg. per 100 cc. A blood culture was negative for pathogens. Venous pressure was 186 mm. of water. The circulation time (dehydrocholic acid) was 29 minutes, and vital capacity 1,900 and 2,200 cc. Urinalysis showed the specific gravity to be 1.022. The urine showed an acid reaction, a 2+ reaction for albumin and a negative reaction for sugar and acetone. The sediment contained many white blood cells and 1 red blood cell per high-power field. A roentgenogram of the chest was reported as indicating no pulmonary congestion and no decrease in cardiac size. An electrocardiographic tracing made shortly before death was interpreted as showing (1) sinus tachycardia; (2) right axis deviation with prominent R wave in Lead V_1 and S wave in Lead V_6, suggesting cor pulmonale, and (3) marked interference. A smear from the sternal bone marrow revealed 2.7% plasma cells and a myeloid-erythroid ratio of 1 : 2 and was interpreted as displaying erythroid hyperplasia. A biopsy specimen of an axillary lymph node revealed lipomelanotic reticular hyperplasia.

The patient was afebrile on this occasion. The edema of the feet and ankles disappeared by the seventh day, at which time the blood pressure was 136/108. She appeared the same until one hour after the sternal marrow aspiration on the 10th day. At this time she became excited and apprehensive; the pulse rate was 100 and the blood pressure 140/120. She was given oxygen, aminophylline, and papaverine hydrochloride. A protodiastolic gallop rhythm developed. She had a right-sided clonic convulsion, became unconscious, and died 125 minutes after the sternal puncture.

Synopsis of Autopsy Observations (two hours after death).—Gross Observations: The nail beds were markedly cyanotic, and the neck veins were prominently distended. There was 200 cc. of a straw-colored fluid in the peritoneal cavity. The liver edge was 8 cm. below the right costal margin in the midclavicular line. There were multiple petechiae in the serosa of the small bowel and numerous small lymph nodes in the mesentery. The pleural and pericardial cavities were empty. The pleural surfaces were smooth throughout and the lungs collapsed within their respective spaces. The mediastinal lymph nodes were numerous, small, and soft. The blood throughout the body failed to clot after 24 hours.

The heart weighed 320 gm. The right auricle and ventricle were prominently dilated. The wall of the right ventricle varied between 0.7 and 0.9 cm. in thickness. The left ventricle averaged 1.5 cm. in thickness. The trabeculae corneae and papillary muscles of the right ventricle were thickened. The valves were unaltered. The coronary arteries were normal. The right lung weighed 260 gm., the left, 210 gm. The lungs were fully expanded on opening of the chest and subsequently collapsed readily. They felt light, were normally crepitant, and contained no demonstrable fluid. On section the cut surfaces were normal. The larger pulmonary arteries revealed a slight degree of atherosclerosis. The liver weighed 1,200 gm. and had the nutmeg appearance grossly. The spleen weighed 200 gm. The gastrointestinal tract, gall bladder, and pancreas were normal. The right kidney weighed 195 gm., the left, 200 gm. There were a few pelvic petechiae; otherwise no gross abnormalities were noted. The adrenal glands and urinary bladder were normal. The bone marrow was plentiful. The brain, which weighed 1,130 gm., was grossly unaltered.

Microscopic Observations: The myocardium was normal. In the lungs the alveolar walls and spaces were essentially normal, but the smaller blood vessels were markedly altered throughout sections taken from all lobes. The commonest change involving small arteries consisted of a marked thickening of the wall with a corresponding narrowing of the lumen (Figs. 6*B* and 7*A*). The lumina of these vessels were usually eccentric in location. The thickening appeared to be due mainly to a proliferation of subendothelial connective tissue (Fig. 7*A*). Atrophy of the media

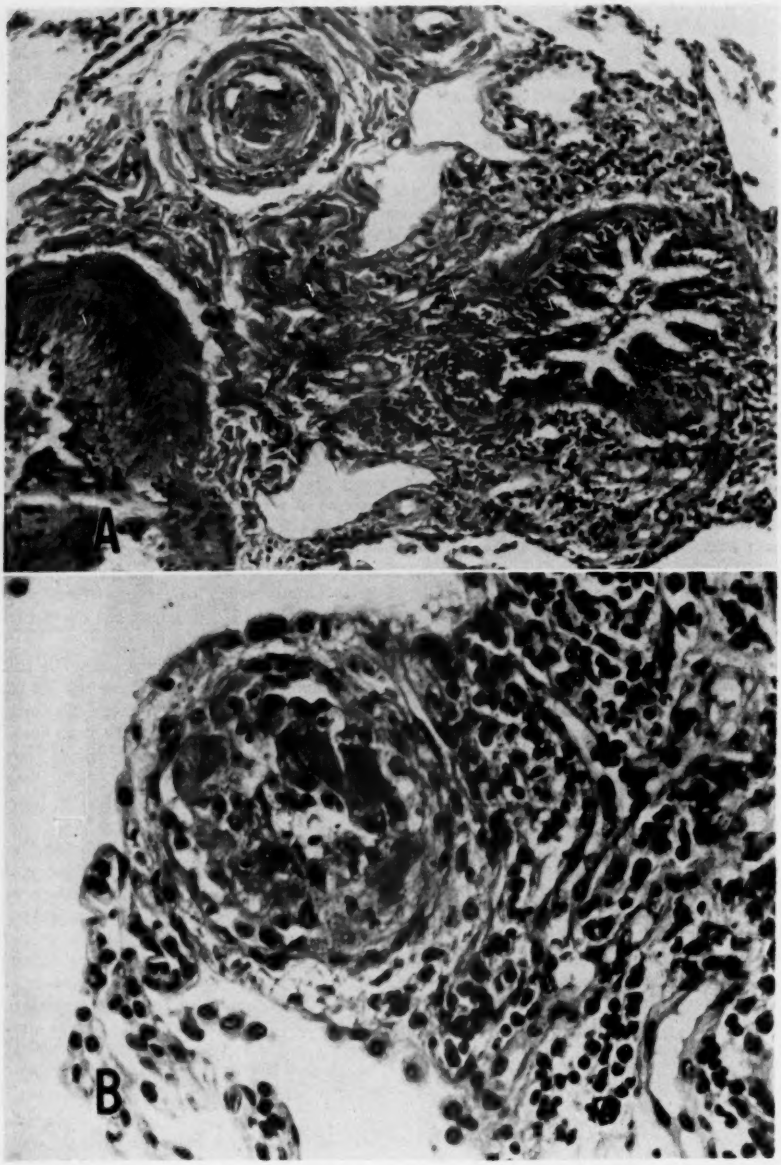

Fig. 5 (Case 2).—*A*, upper vessel is occluded by a proteinaceous thrombus. There are endothelial proliferation and moderate intimal thickening. Lower arterial segment shows slight intimal thickening. There is also peribronchiolitis. × 150. *B*, another vessel occluded by a protein-like thrombus which has been partly invaded by endothelial cells. Inflammation about this vessel is evident. × 400.

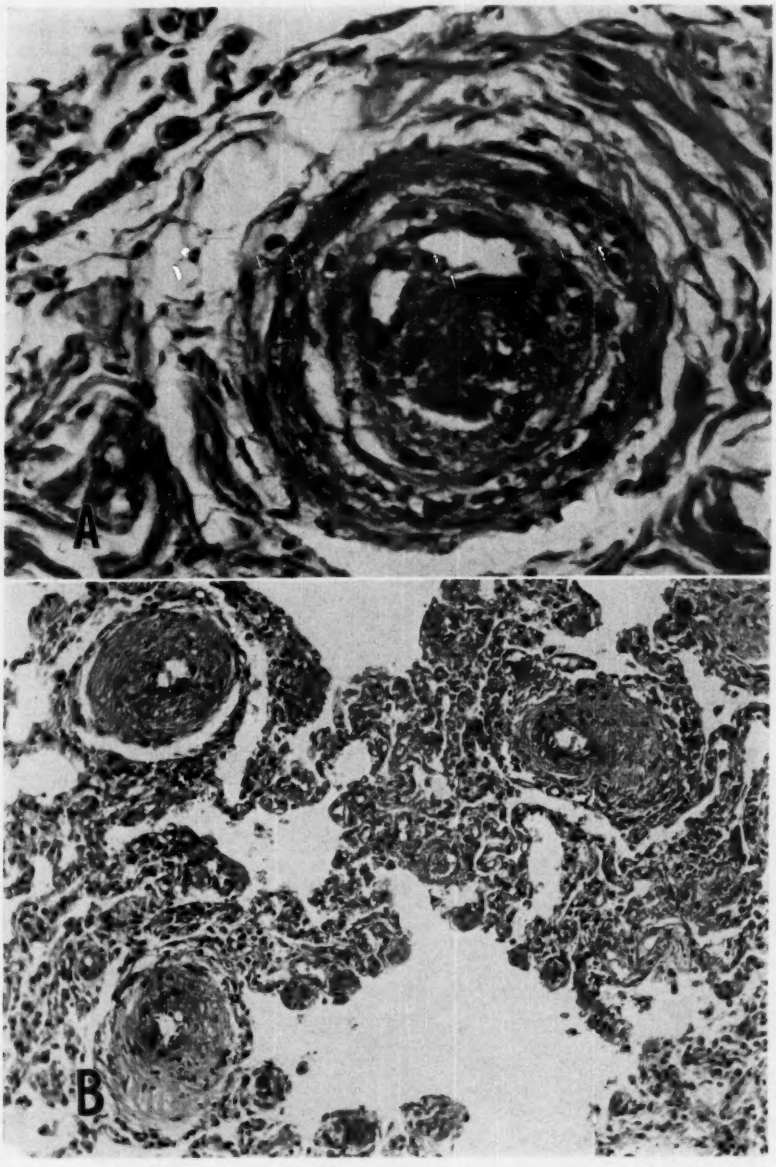

Fig. 6 (Case 2).—*A*, a higher magnification of occluded vessel in Figure 5*A*. Partial invasion of proteinaceous thrombus by endothelial cells is depicted. × 400. *B*, several small arteries showing fibrous thickening of their walls and narrowed, eccentric lumina. Media is either atrophic or replaced by fibrous tissue. × 110.

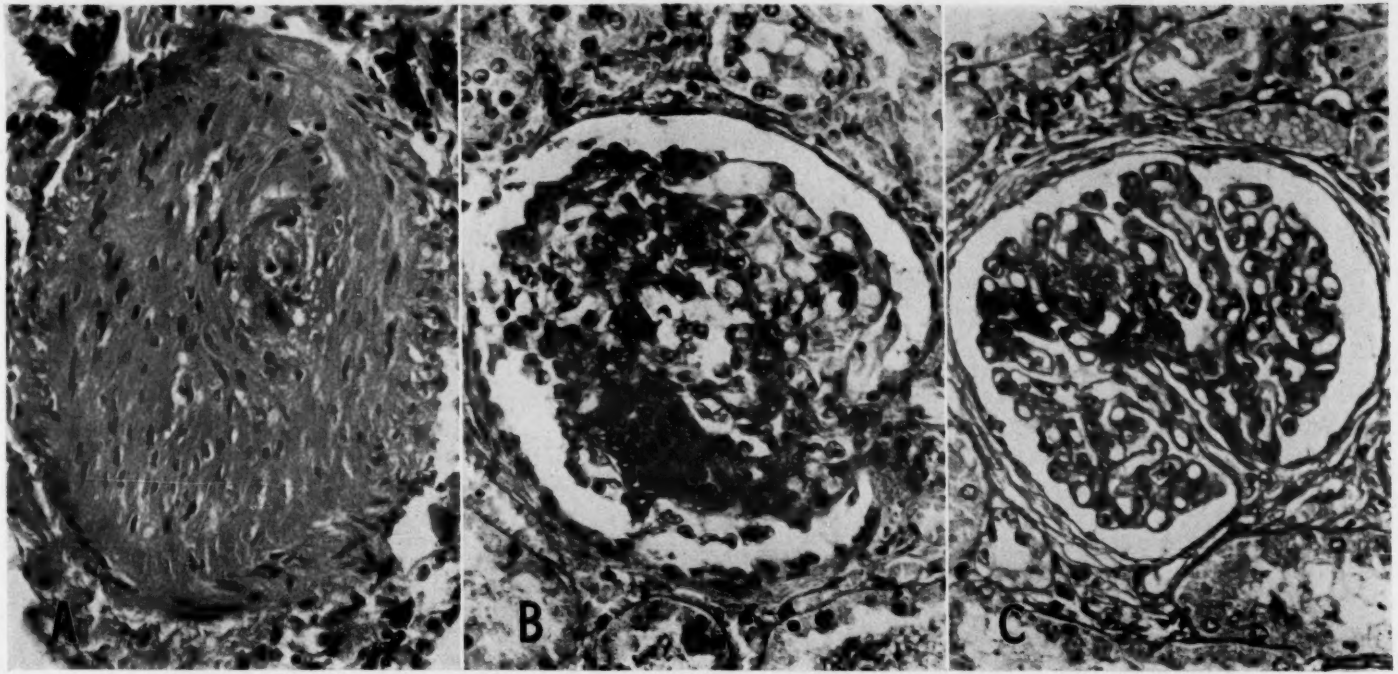

Fig. 7 (Case 2).—*A*, marked endarteritis obliterans. Media is atrophic, and intima is eccentrically thickened with fibrous tissue. ×400. *B*, glomerulitis. This is proliferation of segments of glomerulus with diminution in vascularity. There are also adhesions between lobules and capsule. × 400. *C*, there is thickening of basement membrane resembling the "wire-loop" lesion. One lobule is necrotic. × 400.

and diffuse fibrosis of the arterial wall were also noted (Fig. 7*A*). Another prominent change involving small vessels consisted of occlusion of the lumina by a special type of thrombotic mass. This mass stained pink with eosin and in some vessels was finely granular, while in others it had a coarse, lumpy appearance (Figs. 5 and 6*A*). The endothelium of the blood vessel proliferated around and into these masses. The occlusive masses appeared to involve both small arteries and venules. They did not conform with the appearance of regular emboli or thrombi or thrombocyte thrombi, but instead resembled precipitated protein, such as one sees in renal tubules. About certain of the obstructed vessels an accumulation of inflammatory cells, lymphocytes, neutrophils, and macrophages was seen (Fig. 5*B*). Around scattered bronchioles there was a similar collection of inflammatory cells which frequently entered into regional alveolar walls (focal pneumonitis).

The liver revealed marked hyperemia and central necrosis. The gall bladder was edematous. The kidneys showed focal glomerulitis. Some glomeruli revealed an increased cellularity, a diminished vascularity, and adhesions between the glomerular lobules and Bowman's capsule (Fig. 7*B*). Others showed a thickening of the basement membrane and intercapillary areas and focal necrosis (Fig. 7*C*). The tubules contained scattered casts and a granular precipitate. The lymph nodes contained numerous plasma cells, which had partly replaced the architecture. The

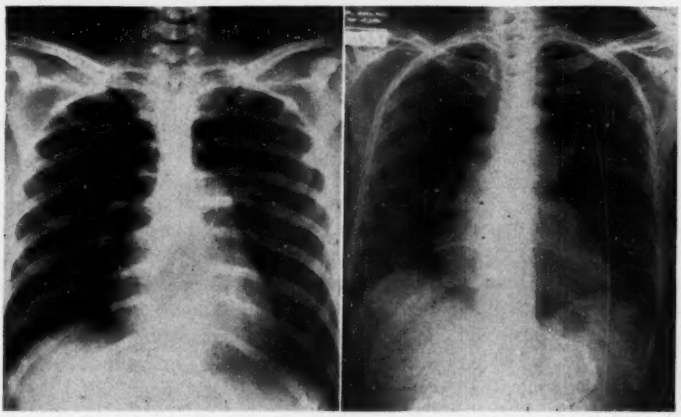

Fig. 8.—Roentgenograms of the chest of each patient. Notice normal lung fields. In first case (left) there is a prominent pulmonary artery segment. In second case (right) there is generalized cardiomegaly.

smears from various sites of bone marrow revealed 15 to 20% plasma cells, some of which were immature (plasmablasts, proplasmacytes). Plasma cells were also plentiful in the gastrointestinal tract. No abnormalities were noted in the brain.

Diagnoses.—The anatomical diagnoses were as follows: (1) plasmacytosis [4]; (2) widespread pulmonary vascular sclerosis (endarteritis); (3) pulmonary atherosclerosis; (4) multiple, small,

4. Bing, J., and Plum, P.: Serum Proteins in Leucopenia, Acta med. scandinav. **92**:415-428, 1937. Carter, J. R.: Plasma Cell Hyperplasia and Hyperglobulinemia in Trichinosis, Am. J. Path. **25**:309-322, 1949. Robertson, T.: Plasmacytosis and Hyperglobulinemia as Manifestations of Hypersensitivity: A Postmortem Study of 2 Cases with Hypersensitivity Probably to Sulfadiazine, Am. J. Med. **9**:315-329, 1950. Good, R. A., and Campbell, B.: Relationship of Bone Marrow Plasmacytosis to the Changes in Serum Gamma Globulin in Rheumatic Fever, ibid. **9**:330-342, 1950. Groth, H.: Serum Protein and Plasma Cells in Rubeola, Finska läk-sällsk. handl. **80**:674-680, 1937. Kolouch, F.; Good, R. A., and Campbell, B.: The Reticuloendothelial Origin of Bone Marrow Plasma Cells in Hypersensitive States, J. Lab. & Clin. Med. **32**:749-755, 1947. Fadem, R. S., and McBirnie, J. E.: Plasmacytosis in Diseases Other Than the Primary Plasmacytic Diseases, Blood **5**:191-200, 1950.

proteinaceous pulmonary thrombi, with endothelial organization; (5) right ventricular hypertrophy and dilatation; (6) hyperglobulinemia and cryoglobulinemia; (7) focal bronchiolitis and interstitial pneumonitis; (8) generalized arteriolosclerosis; (9) passive hyperemia of liver with central necrosis; (10) focal glomerulitis; (11) minimal ascites.

COMMENT

The two cases herein reported had the following clinical and morphologic features in common: (1) right heart failure, with exertional dyspnea and cyanosis being prominent in the first case and a hacking cough and cyanosis occurring in the second case; (2) mild polycythemia, as revealed by the red blood cell count and hemoglobin concentration; (3) prominent hypertrophy and dilatation of the right ventricle; (4) widespread pulmonary vascular sclerosis, particularly of the endarteritic type, similar to what has been termed primary pulmonary vascular sclerosis; (5) occlusive masses in many small pulmonary arteries; in the one instance these were obviously either embolic or thrombotic, while in the other they seemed to represent precipitated protein; (6) normal lungs on the roentgenologic and gross examinations; (7) focal pneumonitis, usually near the vascular occlusive masses; (8) passive hyperemia of the viscera; (9) centrolobular damage of the liver; (10) mild ascites, and (11) a fairly rapid clinical course, lasting nine and six months, respectively. With these common features one feels reasonably certain in concluding that the entity portrayed was similar in the two cases.

The one outstanding difference between the two cases was a morphologic one, namely, a difference in composition of the masses occluding the small pulmonary blood vessels. These masses, however, were prevalent, thus appearing as a major common feature.

In Case 1 it could not be settled by morphologic means whether the occlusive masses in the pulmonary vessels were embolic or thrombotic in origin. Just as in the report of Castleman and Bland,[10] the embolic explanation appeared plausible since a source for emboli was demonstrated in the pelvic veins and a recent large embolus was encountered in the lower lobe of the right lung. This explanation suffers from the necessity of considering either that the emboli arose as minute structures or that larger emboli were shattered within the circulation on each occasion and were disseminated within the lungs as tiny masses. In support of the latter possibilities there is the observation by Brenner [10] indicating the existence of small peripheral pulmonary emboli in 28 of 100 consecutive autopsies when these structures were closely searched for. The difficulties in distinguishing between pulmonary emboli and thrombi are well discussed by Brenner and Cummine and Lyons.[5] The latter workers believed that primary pulmonary thrombosis is commoner than ordinarily considered.

The first patient displayed another feature of possible theoretical importance. The first major symptom, left vocal cord paralysis, occurred shortly after the delivery of a child. An explanation for this disturbance, as discussed by Dolowitz and Lewis,[6] is impingement on the recurrent laryngeal nerve by a prominent pulmonary artery. At the time of the paralysis the roentgenologist suggested the pres-

5. Cummine, H. G., and Lyons, R. N.: A Study in Intravascular Thrombosis with Some New Conceptions of the Mechanism of Coagulation, Brit. J. Surg. **35**:337-363, 1948.

6. Dolowitz, D. A., and Lewis, C. S.: Left Vocal Cord Paralysis Associated with Cardiac Disease, Am. J. Med. **4**:856-862, 1948.

ence of a prominent pulmonary artery segment. It must be considered that disturbances in the pulmonary vasculature had occurred prior to the development of this symptom. The recent parturition suggests the possibility of amniotic fluid embolization.[7] Although there was no immediate clinical indication of this complication, the possibility of a marked degree of amniotic fluid embolization, plus a superimposed diffuse pulmonary thrombosis along the lines discussed by Schneider,[8] cannot be entirely dismissed. Two morphologic features, the diffuse distribution of tiny occlusive vascular masses and the presence of lipophages within certain alveoli bordering the nearby focal pneumonitis, are in keeping with this hypothesis. The renal infarct and transient hemiplegia suggest thrombosis elsewhere in the body. Moreover, as presented in a separate report,[2] human amniotic fluid injected intravenously into the rabbit over a prolonged period evokes pulmonary vascular sclerosis and a focal granulomatous pneumonitis.

It appears evident from these considerations that a characterization of the occlusive masses in the first case as distinctly embolic or thrombotic was not possible. In the second case the masses occluding many pulmonary vessels did not conform with the composition of classic emboli or thrombi; instead they were reddish-granular and resembled precipitated protein. The early phases of the organization of these thrombi were characterized by an irregular invasion of their substance with endothelial cells. Since the patient had a prominent degree of hyperglobulinemia associated with a high cryoglobulin content,[9] the possibility of the in vivo flocculation of this unstable globulin becomes apparent. It is known that this globulin, which precipitates in a cold environment, may have a wide thermal amplitude, a feature it shares with the cold agglutinins. At times, the sensitivity to cold approaches body temperature.[9b] In vivo flocculation of this globulin has been suggested by its association with the Raynaud phenomenon [10] and a purpuric state.[11] Whether conditions in the lungs may in some cases be such as to effect a flocculation of this globulin is not known, but this is an attractive, if as yet unproved, possibility. No other explanation for the phenomenon observed in this patient was forthcoming. The syndrome depicted by the patient did not conform with that known as "thrombotic thrombocytopenia," [12] another condition in which proteinaceous thrombi, interpreted as thrombocyte thrombi, occur.

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7. Steiner, P. E., and Lushbaugh, C. C.: Maternal Pulmonary Embolism by Amniotic Fluid as Cause of Obstetric Shock and Unexpected Deaths in Obstetrics, J. A. M. A. **117**:1245-1254 (Oct. 11); 1340-1345 (Oct. 18) 1941.

8. Schneider, C. L.: "Fibrin Embolism" (Disseminated Intravascular Coagulation) with Defibrination as One of the End Results During Placenta Abruptio, Surg., Gynec. & Obst. **92**:27-34, 1951.

9. (*a*) Footnote 3. (*b*) Hill, R. M.; Dunlap, S. G., and Mulligan, R. M.: A Cryoglobulin Present in High Concentration in the Plasma of a Case of Multiple Myeloma, J. Lab. & Clin. Med. **34**:1057-1070, 1949.

10. Hansen, P. F., and Faber, M.: Raynaud's Syndrome Originating from Reversible Precipitation of Proteins, Acta. med. scandinav. **129**:81-100, 1947.

11. Footnote 3. Lucey, H. C.; Leigh, E.; Hoch, H.; Marrack, J. R., and Johns, R. G. S.: Study of a Case of Purpura Associated with Bone Changes and Formation of a Gel in the Serum on Cooling, Brit. J. Exper. Path. **31**:380-389, 1950.

12. Singer, K.; Motulsky, A. G., and Shanberge, J. N.: Thrombotic Thrombocytopenic Purpura, Blood **5**:434-448, 1950. Muirhead, E. E.; Crass, G., and Hill, J. M.: Diffuse Platelet Thromboses with Thrombocytopenia and Hemolytic Anemia (Thrombotic Thrombocytopenic Purpura), Am. J. Clin. Path. **18**:523-532, 1948.

The hyperglobulinemia of Case 2 was associated not only with cryoglobulinemia but also with a prominent plasma cell population in the bone marrow and lymph nodes, focal glomerulitis, and a thickening of the glomerular basement membrane which resembled the "wire-loop" lesion. Incipient myeloma, as described by Waldenström,[13] was considered clinically. In view of the combination of the clinical and morphologic features, this diagnosis does not appear tenable. Teilum [14] has studied this question and has concluded that a series of conditions with a likely hypersensitive background evokes this combination of disturbances. The number of reports emphasizing the association of hyperglobulinemia and plasmacytosis, particularly of the bone marrow, has increased markedly in recent years.[4] Hypersensitivity is frequently considered as the common background in these varied states. The present case appears to constitute another example of the condition termed plasmacytosis with hyperglobulinemia.

This case was also complicated by syphilis. Two courses of antisyphilitic treatment were given. The occurrence of pulmonary vascular sclerosis and syphilis presents the question of Ayerza's disease.[15] At an earlier era it is likely that such a diagnosis would have been appended to this case. In recent years the term Ayerza's disease has been mostly superseded by the term Ayerza's syndrome,[16] at least partly in an attempt to minimize the syphilitic origin of the pulmonary lesion, for modern interpretation does not consider syphilis as an outstanding cause of pulmonary endarteritis. The patient had Ayerza's syndrome, but the absence of syphilitic lesions outside the lungs and the presence of the combination of plasmacytosis, hyperglobulinemia, and glomerulitis do not support syphilis as the direct causative factor. Whether syphilis or its treatment initiates mechanisms, possibly of a hypersensitive nature, which may effect these disturbances cannot be stated at present.

In reviewing the available literature dealing with the subject of pulmonary vascular sclerosis, it became apparent, as discussed in the introduction, that embolic and/or thrombotic masses within pulmonary arteries have been observed in association with the vascular thickening on several occasions. Recently, Mallory [17] has discussed an additional case displaying this striking association. Harrison [1w'] has demonstrated the occurrence of acute arteritis and a transient endarteritis by a direct experimental approach, namely, the intravenous injection of small emboli consisting mainly of fibrin. It was, therefore, considered worth while to repeat Harrison's observations and to attempt to extend them. As reported separately,[2] the prolonged intravenous injection of embolic masses in rabbits has been followed by the development of acute pulmonary arteritis, healed arteritis, and widespread pulmonary endarteritis causing a narrowing of many pulmonary arteries. The last-

13. Waldenström, J.: Incipient Myelomatosis or "Essential" Hyperglobulinemia with Fibrinogenopenia, a New Syndrome? Acta. med. scandinav. **117**:216-247, 1944.

14. Teilum, G.: Allergic Hyperglobulinosis and Hyalinosis (Paramyloidosis) in Reticulo-Endothelial System in Boeck's Sarcoid and Other Conditions: Morphologic Immunity Reaction, Am. J. Path. **24**:389-407, 1948; Hyperglobulinemia, Periarterial Fibrosis of Spleen, and Wire Loop Lesion in Disseminated Lupus Erythematosus in Relation to Allergic Pathogenesis, ibid. **24**:409-427, 1948.

15. Martz, C. A., cited by Konstam.[1c']

16. Ayerza's Syndrome, Editorial, Lancet **2**:833, 1929.

17. Mallory, T. B., in discussion on Cor Pulmonale, Cabot Case 37251, New England J. Med. **244**:949-951, 1951.

named lesions resemble closely those observed in the cases herein reported. Karsner and co-workers [18] had earlier demonstrated similar lesions following the experimental injection of Lycopodium seeds. Van Glahn [18] produced a granulomatous pulmonary vascular sclerosis by the injection of cotton fibers. Wartman, Hudson, and Jennings [19] also have produced pulmonary endarteritis in the rabbit by means of the intravenous injection of blood clots. Our data appear to represent a confirmation of their work, although we were not aware of its being in progress.

There are increasing observations supporting the concept that minute occlusions of pulmonary arteries effect pulmonary vascular sclerosis. The evidence includes the morphologic association of thrombotic or embolic occlusions and pulmonary endarteritis in the human being and a multiplicity of approaches which experimentally bring about similar changes. The term "thromboembolic pulmonary vascular sclerosis or endarteritis" is suggested for this form of pulmonary vascular sclerosis. This term may be considered to represent a modification of Tschistowitsch's designation "chronic pulmonary thromboendarteritis." [19]

It is not meant to imply by the term thromboembolic pulmonary endarteritis or vascular sclerosis that the fundamental cause of the sclerosis is explained by its association with occlusive masses. For instance, the important question whether the sclerosis is mainly preembolic or postembolic or thrombotic remains to be answered.

Pulmonary hypertension has been considered a causative factor in pulmonary vascular sclerosis,[20] just as systemic hypertension has been implicated in discussions on the pathogenesis of peripheral arteriolosclerosis.[21] The association of hypertension and vascular sclerosis, although seemingly an intimate one, need not imply a direct cause-and-effect relationship. Reasons for a possible dissociation between experimental peripheral hypertension and peripheral arteriolosclerosis have been discussed elsewhere.[22] In the lungs the question of the nutritional status of the arterial wall in the presence of multiple arterial occlusions requires additional consideration. It is conceivable that the pulmonary hypertension, when it exists, may represent a by-product of the basic condition that alters the nutritional status of the arterial wall, thereby culminating in injury to the arterial wall, followed by the workings of the repair process which acts through the means of endarteritis or vascular sclerosis. According to the present state of knowledge, it appears as plausible to consider the nutritional hypothesis in the fundamental causation of the sclerosis as the concept that hypertension per se represents the basis for the sclerosis.

18. Van Glahn, W. C., and Hall, J. W.: The Reaction Produced in the Pulmonary Arteries by Emboli of Cotton Fibers, Am. J. Path. **25**:575-584, 1949.

19. Wartman, W. B.; Hudson, B., and Jennings, R. B.: Experimental Arterial Disease: I. The Reaction of the Pulmonary Artery to Minute Emboli of the Blood Clot, Circulation **4**:747-755, 1951; II. The Reaction of the Pulmonary Artery to Emboli of Filter Paper Fibers, ibid. **4**:756-763, 1951.

20. Moschcowitz, E.: Vascular Sclerosis, New York, Oxford University Press, 1942.

21. Byrom, F. B., and Dodson, L. F.: The Causation of Acute Arterial Necrosis in Hypertensive Disease, J. Path. & Bact. **60**:357-368, 1948.

22. Muirhead, E. E.; Turner, L. B., and Grollman, A.: Hypertensive Cardiovascular Disease: Vascular Lesions of Dogs Maintained for Extended Periods Following Bilateral Nephrectomy or Ureteral Ligation, Arch. Path. **51**:575-592 (June) 1951; Hypertensive Cardiovascular Disease: Nature and Pathogenesis of Arteriolar Sclerosis Induced by Bilateral Nephrectomy as Revealed by Study of Its Tinctorial Characteristics, A. M. A. Arch. Path. **52**:266-279 (Sept.) 1951.

SUMMARY

Two cases of Ayerza's syndrome and with common pulmonary morphologic features are presented. The pulmonary vascular sclerosis (endarteritis) depicted may have been considered of the primary type were it not for the presence of numerous occlusive masses within small pulmonary arteries. These occlusive masses in the first case were either embolic or thrombotic. In the second case the masses appeared to be proteinaceous. This patient had a marked hyperglobulinemia, cryoglobulinemia, plasmacytosis, and glomerulitis. To our knowledge, this represents the first instance recorded of cryoglobulinemia with pulmonary vascular sclerosis. It is suggested that the occlusive masses represented are in vivo flocculation of this unstable globulin.

There is a growing body of evidence supporting the view that occlusive masses in small pulmonary arteries cause pulmonary vascular sclerosis. This explanation is preferred for the cases reported herein. The term "thromboembolic pulmonary endarteritis" is suggested for this form of pulmonary vascular sclerosis.

It is emphasized that the presence of vascular occlusion does not explain the fundamental cause of the vascular sclerosis. Although pulmonary hypertension has been considered as the cause of pulmonary endarteritis, it appears as plausible that alterations in the nutritional status of the arterial wall are of fundamental importance. Such a hypothesis considers the hypertension, when present, as a by-product of the vascular occlusion and relates the sclerosis to the injury plus the operation of the repair process as it affects blood vessels.

The difficulties in explaining various features of these unique cases are discussed.

USE OF QUINIDINE IN TREATMENT OF CHRONIC AURICULAR FIBRILLATION

Results Obtained in a Series of One Hundred Fifty-Five Patients

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MARVIN ROSENBLUM, M.D.
AND
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WINSTON-SALEM, N. C.

DURING recent years, considerable interest in the management of patients with chronic auricular fibrillation has developed. Previously, it was believed that this arrhythmia was merely a manifestation of the unfavorable progress of severe heart disease, and that in itself it did not materially affect the health of the patient or interfere with his cardiac efficiency.[1] Now, however, abundant evidence, both clinical and experimental, supports the view that auricular fibrillation does have deleterious effects upon the circulation.

In experimental animals, several groups of investigators [2] have demonstrated a decrease in cardiac output during auricular fibrillation. Blumgart and Weiss,[3] as well as Stewart and his associates,[4] have reported that the rate of blood flow is reduced by as much as 20 to 68%. After the restoration of sinus rhythm, the blood flow returned to normal. Blood gas studies during and after auricular fibrillation

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Read before the Section on Experimental Medicine and Therapeutics at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 14, 1951.

1. DeGraff, A. C., and Lingg, C.: The Course of Rheumatic Heart Disease in Adults: The Influence of Auricular Fibrillation on the Course of Rheumatic Heart Disease, Am. Heart J. **10**:630-642 (June) 1935. Stroud, W. D.; Laplace, L. B., and Reisinger, J. A.: The Etiology, Prognosis, and Treatment of Auricular Fibrillation, Am. J. M. Sc. **183**:48-60 (Jan.) 1932.

2. Stewart, H. J., and Gilchrist, A. R.: Studies on the Effect of Cardiac Irregularity on the Circulation: II. The Estimation of Cardiac Output in Dogs Subject to Auricular Fibrillation, J. Clin. Invest. **5**:335-342 (Feb.) 1928. Stewart, H. J.; Deitrick, J. E.; Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms: Observations Relating to (Part I) Rhythms Associated with Rapid Ventricular Rate and to (Part II) Rhythms Associated with Slow Ventricular Rate, ibid. **17**:449-463 (July) 1938.

3. Blumgart, H. L., and Weiss, S.: Clinical Observations on the Velocity of Blood Flow in Auricular Fibrillation and Emphysema, Tr. A. Am. Physicians **41**:294-296, 1926; Studies on the Velocity of Blood Flow: IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, J. Clin. Invest. **4**:173-197 (June) 1927.

4. Stewart, H. J.; Crawford, J. H., and Hastings, A. B.: The Effect of Tachycardia on the Blood Flow in Dogs: I. The Effect of Rapid Irregular Rhythm as Seen in Auricular Fibrillation, J. Clin. Invest. **3**:435-447 (Dec.) 1926.

indicate that cardiorespiratory efficiency is greater with a normal sinus rhythm, even though the ventricular rate is slower during auricular fibrillation.[5] Of additional interest is the work of Blumgart,[6] who has shown that in patients with auricular fibrillation the increase in ventricular rate following exercise is greater, and the delay in return to normal is longer, than in those with a sinus rhythm. In dogs with auricular fibrillation, Lands and his co-workers [7] have found a disproportionate rise in central venous pressure after exercise.

Such observations attest to the fact that auricular fibrillation has an adverse effect on circulatory dynamics and indicate that continuation of this rhythm in an already failing heart is detrimental to the patient. This finding, aside from the distress which palpitation causes the patient although digitalized, has led us to make an attempt to restore normal sinus rhythm in the majority of our patients with chronic auricular fibrillation.

Although quinidine therapy has been recommended since 1914 for the management of this disorder,[8] there still exists a diversity of opinion regarding the indications for this drug and the method of administering it. Contraindications frequently mentioned include advanced age, auricular fibrillation of long duration, severe conduction defects, cardiac enlargement, congestive heart failure, and subacute bacterial endocarditis. There does not exist, however, convincing proof that the presence of any factor other than a history of severe reaction to the drug should prevent its use.

The absence of quantitative data and the lack of a uniform therapeutic schedule have contributed to the disagreement regarding the merits of quinidine treatment. In an effort to provide such data, we have determined the plasma concentrations of the drug in patients who were being treated for auricular fibrillation.

CLINICAL MATERIAL AND METHOD

This study was carried out on 155 unselected patients with chronic auricular fibrillation. The condition responsible for the arrhythmia in 50% of the patients was arteriosclerotic heart disease; in 30%, rheumatic heart disease, and, in the remainder, either thyrotoxicosis or miscellaneous conditions. The majority of patients had been digitalized prior to the institution of quinidine therapy.

All patients were hospitalized, and electrocardiograms were made before and after quinidine therapy. Quinidine sulfate was administered orally, and the patients were seen several times daily to evaluate their response to the drug and to detect evidence of toxic reactions. In 105 of these patients, frequent blood samples were drawn for determinations of the plasma quinidine concentration by the method of Brodie and Udenfriend.[9] In most cases, samples were obtained at the time of restoration to normal rhythm; but if normal rhythm was not restored the peak level attained by the dosage schedule employed was determined.

5. Stewart, H. J., and Carter, E. P.: Blood Gases in Auricular Fibrillation and After Restoration of the Normal Mechanism, J. A. M. A. **78**:1751 (June 3) 1922.

6. Blumgart, H. L.: The Reaction to Exercise of the Heart Effected by Auricular Fibrillation, Heart **11**:49-56 (Jan.) 1924.

7. Landis, E. M.; Brown, E.; Fauteux, M., and Wise, C.: Central Venous Pressure in Relation to Cardiac "Competence," Blood Volume and Exercise, J. Clin. Invest. **25**:237-255 (March) 1946.

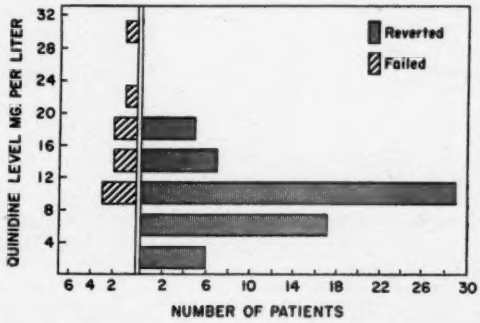
8. Wenckebach, K. F.: Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, Leipzig, W. Engelmann, 1914.

9. Brodie, B. B., and Udenfriend, S.: The Estimation of Quinine in the Human Plasma with a Note on the Estimation of Quinidine, J. Pharmacol. & Exper Therap. **78**:154-158 (June) 1943.

RESULTS

Sinus rhythm was reestablished in 119 of 155 patients with chronic auricular fibrillation (76%). If we eliminate the patients whose therapy was discontinued for reasons beyond our control and the failures, which, in the light of later experience, were believed to have been due to a poorly arranged therapeutic schedule, the percentage of favorable responses is increased to 87%.

The period of quinidine therapy required to restore auricular fibrillation to sinus rhythm ranged from 1 to 18 days and averaged 5.9 days. The average dose given every four hours at the time of reversion was 0.42 gm., and at the same time the mean plasma quinidine content of the patients in whom satisfactory pharmacologic data were obtained was 9.1 mg. per liter. Eight of the patients were known to have passed through a stage of auricular flutter prior to the development of a sinus rhythm, although additional electrocardiograms might have shown this to be a commoner phenomenon. The development of this arrhythmia is not an indication



Plasma quinidine levels at the time of reversion of chronic auricular fibrillation to a sinus rhythm. Peak levels obtained in nine patients unsuccessfully treated are shown on the left.

for discontinuing therapy, since further increases in the dosage of quinidine following this occurrence have resulted in the restoration of a normal rhythm.

As can be seen from the Figure, restoration of a normal sinus rhythm is most apt to occur when the plasma level of quinidine is within a range of 8 to 12 mg. per liter. Correction of the arrhythmia was possible in only four of nine patients requiring plasma levels in excess of 16 mg. per liter. In several instances in which auricular fibrillation recurred after administration of the drug was intentionally discontinued, subsequent therapy again produced reversion to a normal rhythm when plasma levels similar to those obtained during the initial period of treatment were reached.

The value of the blood level as a guide to quinidine therapy is apparent when we consider the fact that only moderate levels of the drug were required to correct the arrhythmia in the majority of cases. In view of the high percentage of failures after a level of 16 mg. per liter was reached, it seems unlikely that a further increase in dosage is indicated in such patients.

In the majority of cases the underlying disease was arteriosclerotic heart disease, rheumatic heart disease, or thyrotoxicosis. Treatment of the last group of

patients was unsatisfactory, and only 3 of the 10 patients were restored to a normal sinus rhythm by quinidine treatment alone; after correction of the thyrotoxicosis, quinidine therapy was almost uniformly successful. Table 1 summarizes the results obtained in patients with arteriosclerotic and rheumatic heart disease. It is evident from this table that the response of these two groups to quinidine therapy was almost identical.

Since age, auricular fibrillation of long duration, and congestive failure are often cited as contraindications to use of quinidine, special attention has been given to the relation between these factors and the results of therapy.

Table 2 summarizes the results obtained in the various age groups. Although there is some variability, as might be found in any biologic experiment, it may be

TABLE 1.—*Comparison of Results of Quinidine Therapy in Chronic Auricular Fibrillation Due to Arteriosclerotic Heart Disease and in That Due to Rheumatic Heart Disease*

Type of Heart Disease	No. of Patients Treated/Reverted	Mean Plasma Level at Time of Reversion, Mg./Liter	Mean Dose at Time of Reversion, Gm./4 Hr.	Mean Duration of Therapy, Days
Arteriosclerotic	60/51 (85%)	8.8	0.40	6
Rheumatic	51/46 (90%)	9.2	0.46	6

TABLE 2.—*Effect of Age upon Results Obtained in Treatment of Chronic Auricular Fibrillation with Quinidine*

Age, Yr.	Number of Patients			Mean at Time of Reversion		
	Treated	Reverted	Analyzed*	Plasma Level, Mg./Liter	Dose, Gm./4 Hr.	Day of Treatment
20-29	10	8	6	8.5	0.37	7
30-39	15	12	7	13.4	0.58	9
40-49	22	20	12	8.0	0.34	3
50-59	25	23	17	9.0	0.54	7
60-69	26	22	17	9.1	0.41	6
70-86	23	19	14	8.2	0.28	5

* Cases in which comparative data are available.

concluded that age itself is not a contraindication to the use of quinidine in the treatment of chronic auricular fibrillation. It is interesting to note that the average dose required was smallest in the oldest age group.

In Table 3 the effect on therapy produced by the duration of fibrillation is analyzed. It is apparent that reversion was accomplished just as easily in patients who had had auricular fibrillation for more than two years as in those who had had auricular fibrillation for less than six months. In three patients abnormal rhythms which had been present for 10, 12, and 15 years reverted readily to normal when plasma concentrations of 10.5, 9.4, and 12.0 mg. per liter, respectively, were attained. Although it is not our purpose to discuss transient auricular fibrillation, it should be mentioned that six patients with this condition responded more quickly than any of the chronic group and showed an average plasma quinidine concentration of only 3.4 mg. per liter at the time of reversion.

Table 4 indicates that difficulty in the restoration of a normal sinus rhythm bore no relationship to the degree of cardiac failure present.

TOXICITY

There are numerous reports in the literature concerning hazards of quinidine to the patient, including the common but relatively harmless toxic effects of the drug. Some authors have even ascribed sudden death to quinidine. In cases of auricular fibrillation, however, one must recognize the severity of the basic cardiac lesion and realize that sudden death is common whether quinidine is used or not. We feel that the dangers of the drug have been overemphasized, especially in regard to idiosyncrasy. Hypersensitivity, evidenced by symptoms of collapse and cardio-

TABLE 3.—*Effect of Duration of Chronic Auricular Fibrillation upon Results of Treatment with Quinidine*

Duration, Mo.	Number of Patients			Mean at Time of Reversion		
	Treated	Reverted	Analyzed*	Plasma Level, Mg./Liter	Dose, Gm./4 Hr.	Day of Treatment
Less than 6	35	32	14	9.1	0.47	5
6-24	42	34	35	9.2	0.40	6
More than 24	37	33	22	8.2	0.38	6

* Cases in which comparative data are available.

TABLE 4.—*Effect of Functional Capacity of Heart upon Results Obtained in Treatment of Chronic Auricular Fibrillation with Quinidine*

Degree of Cardiac Failure*	Number of Patients			Mean at Time of Reversion		
	Treated	Reverted	Analyzed†	Plasma Level, Mg./Liter	Dose, Gm./4 Hr.	Day of Treatment
I	13	11	5	8.3	0.44	6
II	42	35	27	7.5	0.40	6
III	20	17	12	10.0	0.44	7
IV	22	20	5	8.0	0.35	2

* According to the standards of the American Heart Association.
† Cases in which comparative data are available.

respiratory failure developing after the initial dose, was not observed in this series of 155 patients.

The commonest ill effects encountered were gastrointestinal disturbances, including anorexia, nausea, diarrhea, and abdominal cramps. These occurred in 30% of the patients and at widely varying plasma concentrations of the drug, which usually were well within the therapeutic range. These disturbances, as a rule, were mild, and if therapy had been discontinued when they appeared, the arrhythmia would not have been corrected. It seems significant that 11 patients in whom gastrointestinal disturbances were produced by low doses and low plasma concentrations of quinidine failed to show any evidence of a toxic reaction after the doses and plasma concentrations were greatly increased. Although this may have been an adaptive phenomenon, it is possible that the toxic manifestations were due to the rate of increase in the plasma concentration, which is more rapid during the initiation of therapy.

A second group of disturbances, classified as central nervous system and labyrinthine effects, occurred in 15% of the patients and consisted predominantly of diplopia, dizziness, numbness, tinnitus, and deafness. A small group of patients complained of general malaise not related to any of the previously mentioned symptoms. These manifestations, which were never severe enough to necessitate the discontinuance of therapy, were likewise associated with widely varying plasma concentrations of quinidine which usually were within the therapeutic range. Toxic symptoms were less frequent in the aged, probably because of the small dosage required for reversion.

Precipitant hypotensive reactions, which constitute a prime indication for stopping treatment, were not observed in the group. The only fatality which occurred during therapy was that of a 42-year-old patient who had severe congestive failure. He died suddenly during the sixth day of treatment, while plasma concentrations of quinidine were in the range of 10 mg. per liter. An autopsy was not permitted.

There has accumulated considerable evidence indicating that the threat of emboli is diminished when chronic auricular fibrillation is restored to a sinus rhythm.[10] Twenty-three patients in this series gave evidence of having had embolic episodes prior to treatment, whereas this complication developed in only two patients either during or after the administration of quinidine. After the rhythm had reverted to normal, no emboli occurred in those with definite evidence of previous emboli. It was felt that the occurrence of one embolus in a patient with auricular fibrillation was an urgent indication for treatment with quinidine.

THERAPEUTIC SCHEDULE

Data on the clinical pharmacology of quinidine have been reported in a previous paper.[11] Studies have shown that plasma concentrations of the drug reach a maximum within one to three hours after oral administration and begin to decline in four hours. The total amount of quinidine given is not as important as duration of therapy and the size of the individual dose. If constant doses are given at appropriate intervals, a cumulative effect is noted over a period of one to three days, after which a plateau is reached. An increment in dosage then will appreciably raise the plasma concentration. When treatment with the drug is discontinued, a marked drop in the plasma concentration occurs within 24 hours, and in 36 hours almost no quinidine is detectable in the plasma. Since only 6 to 20% of the drug is recovered in the urine and since absorption from the intestinal tract is virtually complete, the assumption is that quinidine is disposed of through metabolic alteration.

In light of the above findings, therapy has been initiated with quinidine being given every four hours, day and night, usually with 0.2 gm. and increasing by 0.1 or 0.2 gm. per dose at the end of each 24- or 48-hour period. Recently the 4 a. m. medication has been omitted, and in its stead the usual amount of quinidine has been given in an enteric-coated tablet along with the regular midnight dose, thus

10. Viko, L. E.; Marvin, H. M., and White, P. D.: A Clinical Report on the Use of Quinidin Sulphate, Arch. Int. Med. **31**:345-363 (March) 1923. Laws, C. L., and Levine, S. A.: Clinical Notes on Rheumatic Heart Disease with Special Reference to the Cause of Death, Am. J. M. Sc. **186**:833-849 (Dec.) 1933.

11. Yount, E. H., and Rosenblum, M.: Studies of Plasma Quinidine Levels in Relation to Therapeutic Effects and Toxic Manifestations, South. M. J. **43**:324-329 (April) 1950.

allowing the patient uninterrupted sleep. Preliminary investigation has indicated that the peak absorption of enteric-coated quinidine occurs within five to six hours after ingestion.[12]

Congestive heart failure, if present, has been treated in the conventional manner prior to the institution of quinidine therapy. We have not hesitated to combine the use of quinidine with that of digitalis, although in this circumstance the dosage of quinidine has been advanced more cautiously.

In many cases the omission of quinidine after restoration of a normal sinus rhythm is followed by the return of auricular fibrillation.[13] Consequently, most of the patients have been given maintenance doses of the drug. The dosage schedule required for restoration of a normal rhythm was generally continued for 24 to 48 hours after reversion, and then the same dose was given every six hours rather than every four hours. If the normal rhythm persisted, further reduction in the individual dose was attempted.

Follow-up data have been exceedingly difficult to obtain, since most of the patients were returned to the care of their local physician. Forty-one of the patients have been followed in our clinic for periods ranging from one month to three years and averaging six months. Of these, only six had lapsed into auricular fibrillation when last seen. The average maintenance dose on a six-hour schedule has been approximately one-half of that necessary for reversion. In the patients for whom complete pharmacologic data were available, the average plasma level required for restoration of a normal sinus rhythm was 10.6 mg. per liter, and for maintenance, 5.3 mg. per liter.

SUMMARY

In 155 unselected patients with chronic auricular fibrillation treated with quinidine, a normal rhythm was restored in 86% of those who were given an adequate therapeutic trial. This was accomplished in an average of six days with a mean dose of 0.42 gm. every four hours and a mean plasma quinidine concentration of 9.1 mg. per liter at the time of reversion.

The duration of fibrillation and the severity of the heart disease did not influence the results of treatment with quinidine. The patients of the oldest age group (70 to 86) responded most readily and to the smallest doses. The only underlying disease which appeared to affect the response to quinidine therapy was thyrotoxicosis; in patients with this condition restoration of normal rhythm was exceedingly difficult until the basic disorder was brought under control.

Pharmacologic data obtained by the measurement of the plasma quinidine concentrations are presented as the basis for the establishment of a successful therapeutic regimen.

Miss Elizabeth Strom gave technical assistance.

The enteric-coated quinidine sulfate tablets were supplied by Eli Lilly & Company, Indianapolis 6.

12. Unpublished data.

13. McMillan, R. L., and Welfare, C.: Chronic Auricular Fibrillation, J. A. M. A. **135**:1132-1135 (Dec. 27) 1947.

ROENTGEN ASPECTS OF PULMONARY ARTERIOVENOUS FISTULA

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AND
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ALTHOUGH it is only thirteen years since the first clinical diagnosis of a pulmonary arteriovenous fistula was made by Smith and Horton,[1] there are now more than 65 proved cases in the medical literature.[2] The clinical features of cyanosis and clubbed fingers, associated with polycythemia and a pulmonary murmur, enable the full-blown clinical syndrome to be easily recognized once the physician is aware of the entity. As emphasized by Goldman,[3] a large proportion of the cases are associated with cutaneous and mucosal hemangiomata and telangiectases of a hereditary nature which probably represent a variant of Rendu-Weber-Osler disease (hereditary capillary telangiectasia). With the study of more cases it has become apparent that the classical clinical picture associated with a large pulmonary arteriovenous shunt and corresponding changes in the peripheral blood does not always occur. One or all of the prominent clinical manifestations may be absent, and the roentgen appearance may be the only positive finding leading to the correct diagnosis.[4] Recognition of this anomaly is of the utmost importance, since it is surgically curable. With these thoughts in mind we have reviewed our roentgenographic experience with eight cases of pulmonary arteriovenous fistulae for the purpose of determining the reliability of the diagnostic roentgen criteria and of discussing the role of roentgenography in the diagnosis of this disease.

Read before the Section on Radiology at the One Hundredth Annual Session of the American Medical Association, Atlantic City, June 15, 1951.

From the Department of Radiology (Dr. Seaman) and the Department of Medicine (Dr. Goldman), Washington University School of Medicine.

1. Smith, H. L., and Horton, B. T.: Arteriovenous Fistula of the Lung Associated with Polycythemia Vera: Report of Case in Which the Diagnosis Was Made Clinically, Am. Heart J. **18**:589, 1939.

2. (*a*) Denolin, H.; Lequime, J., and Jonnart, L.: L'anévrysme artério-veineux pulmonaire, Acta cardiol. **5**:144, 1950. (*b*) Giampalmo, A.: The Arteriovenous Angiomatosis of the Lung with Hypoxaemia, Acta med. scandinav., Supp. 248, 1950, p. 1. (*c*) Yater, W. M.; Finnegan, J., and Giffin, H. M.: Pulmonary Arteriovenous Fistula (Varix), J. A. M. A. **141**:581 (Oct. 29) 1949.

3. Goldman, A.: (*a*) Cavernous Hemangioma of the Lung: Secondary Polycythemia, Dis. Chest **9**:479, 1943; (*b*) Arteriovenous Fistula of the Lung: Its Hereditary and Clinical Aspects, Am. Rev. Tuberc. **57**:268, 1948.

4. Wodehouse, G. E.: Hemangioma of the Lung: A Review of Four Cases Including Two Not Previously Reported, One of Which Was Complicated by Brain Abscess Due to H. Influenzae, J. Thoracic Surg. **17**:408, 1948.

TERMINOLOGY

A number of different terms, including (*a*) pulmonary hemangioma, (*b*) cavernous hemangioma of the lung, (*c*) arteriovenous aneurysm, and (*d*) pulmonary arteriovenous fistula, have been applied to this lesion. Since the clinical significance of this entity is largely determined by the direct shunt of blood from the pulmonary artery to the pulmonary vein without passing through the pulmonary capillary bed, we prefer the term pulmonary arteriovenous fistula. This lesion is not considered to be a true neoplasm and probably represents a congenital vascular malformation.[5a]

CLINICAL FEATURES

During the past 10 years we have seen eight cases of pulmonary arteriovenous fistulae. Four of these have been the subject of previous reports; two were described by Goldman [3b] and two by Lindskog and associates.[5] Since the clinical and pathological features have been adequately described by others, we wish to present only a résumé of the clinical findings, to evaluate the roentgenographic techniques, and to discuss their role in the recognition of this lesion (Table).

Résumé of Clinical Features of Eight Cases of Pulmonary Arteriovenous Fistulae

Patient	Age	Sex	Telangiectases	Family History	Cyanosis	Clubbing	R. B. C. Millions	Murmurs	Hemorrhage
M. A. A.	79	F	Yes	Yes	Yes	Yes	5.56	Yes	Epistaxis
H. D. J.	58	F	Yes	Yes	No	No	3.41	Yes	Epistaxis
L. B.	?	F	Yes	Yes	No	No	3.4	Yes	Hemoptysis
H. W. E.	26	M	Yes	No	Yes	Yes	6.7	Yes	Epistaxis
W. L.*	32	M	No	Yes	Yes	Yes	7.0	Yes	No
E. L.*	22	M	Yes	Yes	Yes	Yes	7-11.0	No	No
D. K.†	56	F	Yes	Yes	No	Yes	4.05	Yes	Epistaxis
B.†	24	M	No	No	No	No	4.86	No	No

* Cases previously reported by Goldman.[3]
† Cases reported by Lindskog and others.[5]

The sex incidence in our series is evenly divided, and the age incidence ranges from 22 to 79 years. The 79-year-old patient was in good health and was referred to the hospital only because of the discovery of an unexplained pulmonary mass during the course of a roentgen examination for virus pneumonia, although she had all of the classical signs and symptoms. Apparently this condition is compatible with longevity, although sudden death from hemorrhage can occur. A patient described by Bowers [6] died of rupture of the fistula into the pleural cavity, and Rodes reported on a patient who died of severe hemoptysis.[7] Among 45 cases collected from the literature by Yater and co-workers,[2c] death in six was thought to have been a direct or indirect result of the pulmonary arteriovenous fistula. Telangiectases and a family history of telangiectasia were present in six of our eight cases. Only one case presented none of the characteristic physical signs or symptoms; the condition was discovered during the course of a routine Army preinduc-

5. Lindskog, G. E.; Liebow, A.; Kausel, H., and Janzen, A.: Pulmonary Arteriovenous Aneurysm, Ann. Surg. **132**:591, 1950.

6. Bowers, W. F.: Rupture of Visceral Hemangioma as Cause of Death, with Report of Case of Pulmonary Hemangioma, Nebraska M. J. **21**:55, 1936.

7. Rodes, C. B.: Cavernous Hemangiomas of the Lung with Secondary Polycythemia, J. A. M. A. **110**:1914 (June 4) 1938.

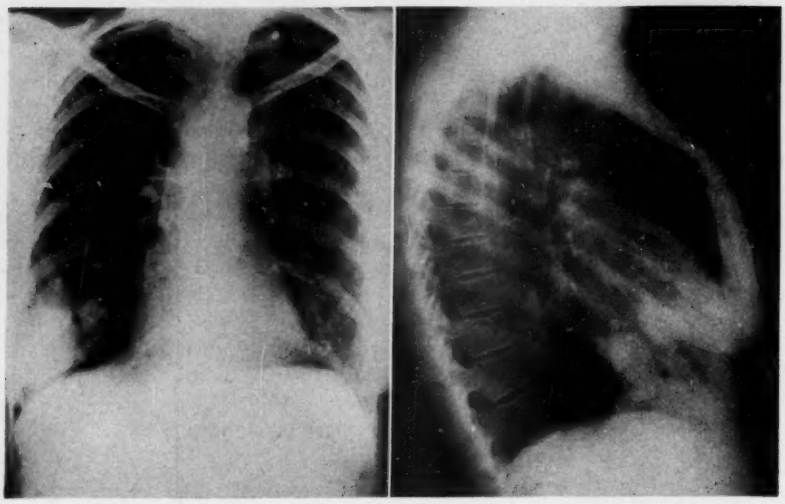

Fig. 1.—Multiple pulmonary arteriovenous fistulae in the right lower lobe. Left, frontal view. Right, lateral view.

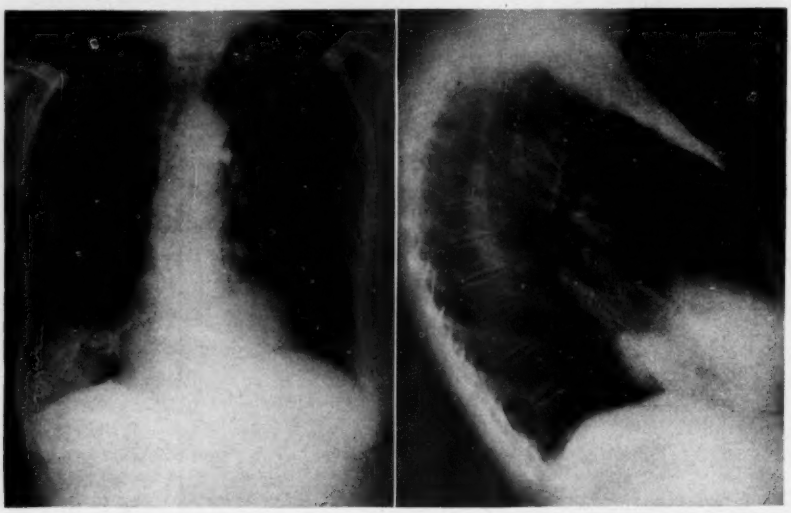

Fig. 2.—Same patient (Fig. 1) twelve years later without significant change in the lesions. Left, frontal view. Right, lateral view.

tion examination. In four patients cyanosis and polycythemia were absent, although three of these patients did have hemorrhagic phenomena which may explain their lowered red blood cell count. Lawrence and Rumel [8] described two cases of pulmonary arteriovenous fistulae, in only one of which there were changes in the peripheral blood. The patient with the polycythemia was found to have an unusually large bronchial artery, which was thought to enter the lesion by anastomosis and to contribute to the filling of the aneurysmal sac. In the studies of Lindskog and colleagues,[5] in which vascular casts were made of three dissected surgical specimens, there was no evidence of a significant contribution from the bronchial arteries. Clubbed fingers occurred in five of our eight patients, and only two did not have a pulmonary murmur. Thus, in 50% of this group of patients there was absence of clubbing, cyanosis, and polycythemia, necessitating greater reliance on the roentgen examination for the recognition of the nature of the underlying pulmonary disease. The usual clinical picture of hemorrhagic hereditary telangiectasia does not include a pulmonary arteriovenous fistula, since the latter occurs in only a small fraction of the cases of Rendu-Weber-Osler disease. Thus, telangiectases are not a reliable diagnostic sign of the presence of a pulmonary arteriovenous fistula, although they should suggest that possibility.

There have been extremely few cases reported in children, despite the fact that this is probably a congenital anomaly. In one of our patients the lesion was present during childhood. It was discovered at the age of 5 years during a roentgen examination for postmeasles pneumonia but was not correctly diagnosed despite the presence of cyanosis, clubbed fingers, and polycythemia.[3a] There was relatively little change in the size or character of the lesion during the subsequent period of 16 years. It is our feeling that these lesions are probably present during childhood but are being overlooked or misinterpreted. Another patient was followed for 12 years without demonstrable change in the pulmonary arteriovenous fistula (Figs. 1 and 2).

ROENTGENOLOGIC FEATURES

Conventional roentgenograms have demonstrated an abnormal pulmonary shadow in every case. Crane, Lerner, and Lawrence [9] reviewed the roentgen findings in 18 cases in the literature and reported that a pulmonary mass was present in all. Similar findings were reported by Giampalmo, who reviewed 57 cases.[2b] The mass is usually lobulated or round with smooth discrete margins and has a predilection for the lower lobes or the right middle lobe. Only 22% of the 45 cases collected by Yater [2c] involved the upper lobe vessels. Upper lobe involvement is even rarer, according to Giampalmo.[2b] Connecting the mass with the hilum are two or more sinuous, linear shadows which represent the dilated afferent and efferent blood vessels (Fig. 3). These vessels are usually larger than the pulmonary vessels in the vicinity, and their course is more tortuous. The veins are more widely dilated than the arteries owing to transmission of arterial pressure directly into the veins.

8. Lawrence, E. A., and Rumel, W. R.: Arteriovenous Fistula of the Lung, J. Thoracic Surg. **20**:142, 1950.

9. Crane, P.; Lerner, H. H., and Lawrence, E. A.: The Syndrome of Arterio-Venous Fistulae of the Lung, Am. J. Roentgenol. **62**:418, 1949.

Thus, the characteristic roentgen picture is one of tortuous band-like shadows communicating with the hilum and with a lobulated soft-tissue tumor in the pulmonary parenchyma. Intrapulmonary hemorrhage resulting from rupture of vessel walls may produce irregular densities and, even, segmental atelectasis obscuring the lesion.[10] Even in this event careful observation of the vessels running from the hilum to the pulmonary opacity may give a clue to the true nature of the underlying lesion.

As was first emphasized by Lindgren,[10] the vascular character of the lesion may be brought out by the use of the Valsalva and the Müller maneuvers. The increase in the intrathoracic pressure produced by the Valsalva test partially interrupts the

Fig. 3.—Laminagraphic section of the same patient as in Figure 1, demonstrating the double band-like shadow extending from the hilum to the parenchymal mass, representing the afferent and efferent vessels.

flow of blood into the lungs and results in a decrease in the size of the vascular sac and the vessels which feed it. The opposite effect may be produced by the Müller test in which the negative intrathoracic pressure is increased, resulting in distention of the malformation with blood. These changes are probably more easily induced in the vessels leading to the fistula because of associated degenerative changes in the walls of the malformation itself. In about one-half of the published cases in which these tests were carried out, a positive response was elicited. Although

10. Lindgren, E.: Roentgen Diagnosis of Arteriovenous Aneurysm of the Lung, Acta radiol. **27**:585, 1946.

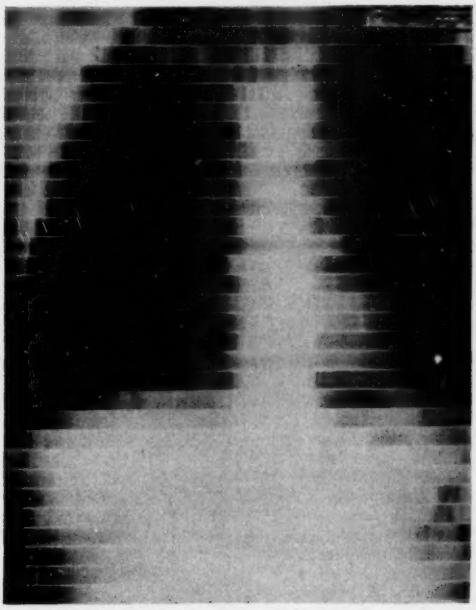

Fig. 4.—Roentgen kymogram of a patient with a pulmonary arteriovenous fistula in the left mid-lung field, demonstrating the presence of expansile pulsation.

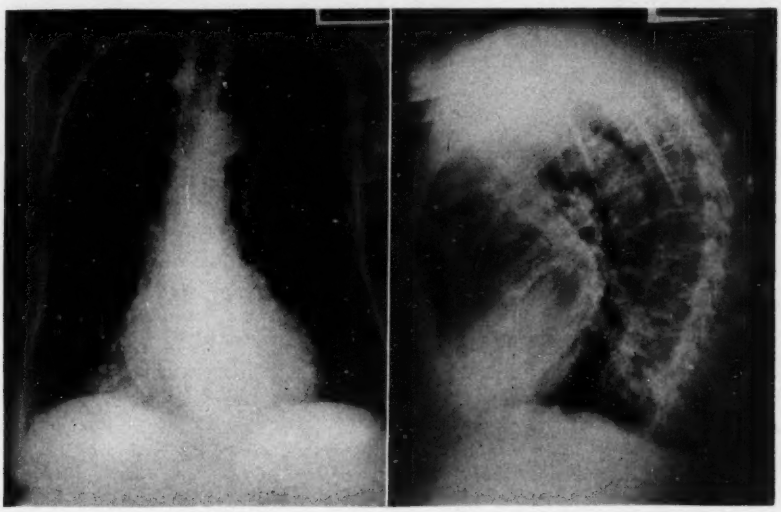

Fig. 5.—Posteroanterior and lateral views of a patient with bilateral pulmonary arteriovenous fistulae.

it was not attempted in all cases, two of our patients showed a change in size of the lesion by this method. This maneuver should be used routinely in the fluoroscopic investigation of all suspected cases of pulmonary arteriovenous fistulae.

Demonstration of the pulsatile nature of the tumor has not been consistently positive and has been described infrequently in the literature, although in many case reports this sign has not been mentioned. In two of our patients pulsations were demonstrated both fluoroscopically and by roentgen kymography (Fig. 4). Small areas of calcification have been noted in the pulmonary mass,[11] but this finding has occurred too infrequently to be of diagnostic significance. The heart is not usually enlarged in instances of pulmonary arteriovenous fistulae, in contrast to the enlargement noted in many cases of arteriovenous fistulae involving the systemic

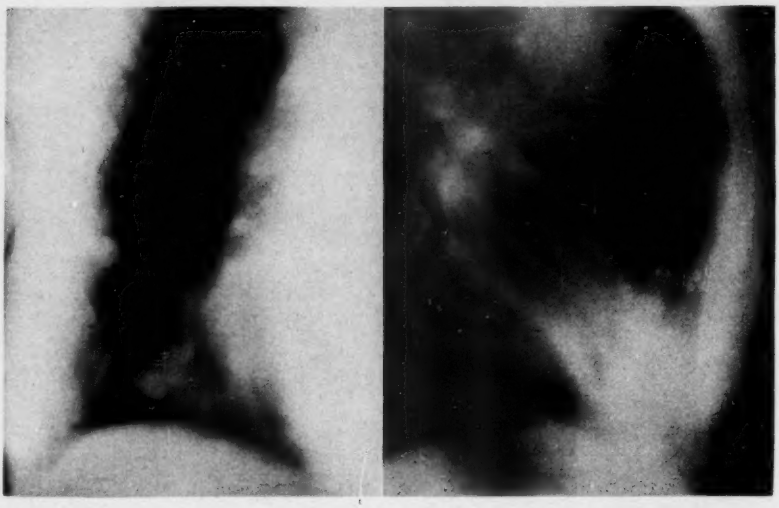

Fig. 6.—Laminagraphic study of the right lung of the same patient as in Figure 5, identifying the lesions in the right lung to be located in the right middle lobe and the anterior basilar segment of the right lower lobe. Left, anteroposterior laminagram. Right, lateral laminagram.

circulation. According to physiological studies of the circulatory dynamics in this condition performed by Friedlich, Bing, and Blount,[12] the resistance of the lung is normally so low that the presence of a shunt does not significantly reduce the over-all vascular resistance unless the resistance of the shunt is unusually low. If the resistance of the pulmonary arteriovenous fistula is low enough to produce a significant reduction of the total pulmonary resistance, the cardiac output will be

11. Jones, I. C., and Thompson, W. P.: Arteriovenous Fistula of the Lung, J. Thoracic Surg. **13**:357, 1944.

12. Friedlich, A.; Bing, R. J., and Blount, S. G.: Physiological Studies in Congenital Heart Disease: IX. Circulatory Dynamics in the Anomalies of Venous Return to the Heart Including Pulmonary Arteriovenous Fistula, Bull. Johns Hopkins Hosp. **86**:20, 1950.

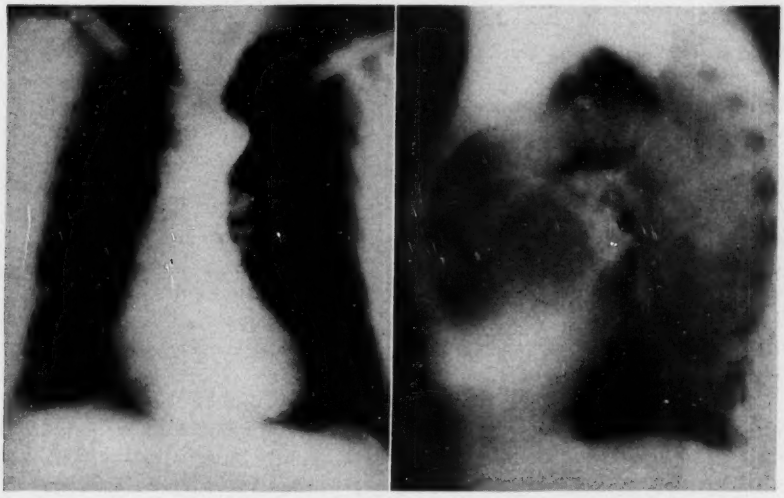

Fig. 7.—Laminagrams of the left lung of the same patient as in Figure 5, identifying another lesion in the anterior segment of the left upper lobe. Left, anteroposterior laminagram in which the lesion is superimposed over the hilar area. Right, lateral laminagram.

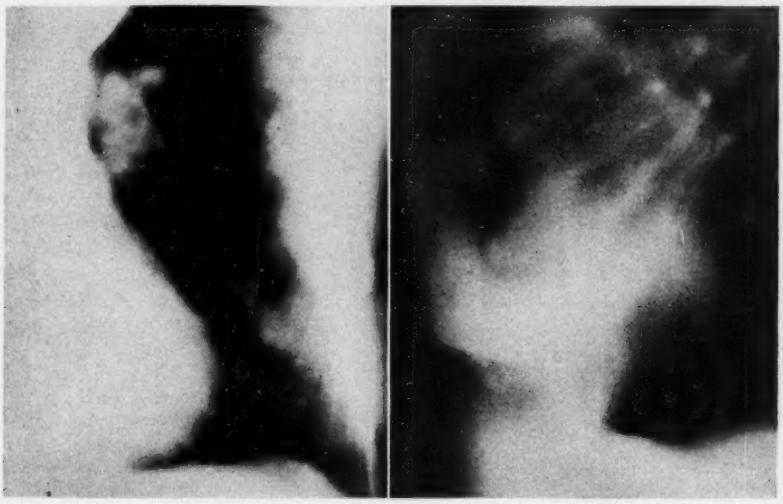

Fig. 8.—Laminagraphic study of the left lung of the same patient as in Figure 5, demonstrating a lesion in the lingula of the left upper lobe. Left, anteroposterior laminagram. Right, lateral laminagram.

increased with resultant cardiac enlargement. This occurred in one of the four patients they studied and has been reported by others.[13]

Lindgren has emphasized the relationship of the mass to the pulmonary vascular shadows as the most significant roentgen diagnostic sign of this lesion. By the use of laminagraphy this relationship can be definitely established (Fig. 3). It should be carried out in both the lateral and the frontal projections whenever such a lesion is suspected. It may also demonstrate lesions not previously recognized in conventional films, as well as indicate the lesion's exact anatomical position in the bronchopulmonary segment. The patient illustrated in Figure 5 had multiple lesions in both lung fields, but only by the use of laminagraphy can one accurately locate each lesion in its correct anatomical position and demonstrate the afferent and efferent vessels.

It is extremely difficult to differentiate pulmonary artery from pulmonary vein in the upper lobe by means of laminagraphy, but this may be done in the lower lobe by virtue of the origin from the parent artery at the hilum or the termination of the vein near the left auricle.

Subpleural lesions may easily escape detection, although diagnostic pneumothorax may prove helpful in demonstrating them. Bronchography is of value by differentiating saccular bronchiectatic cavities filled with secretions which have occasionally simulated the roentgen appearance of arteriovenous fistula.

CARDIOANGIOGRAPHY

For self-evident reasons angiography is the method of choice for proving the vascular character of these lesions and was used successfully by Smith and Horton[1] in confirmation of their first antemortem clinical diagnosis of the condition. However, in 1945, Sisson and associates[14] reported a case in which attacks of unconsciousness and pulmonary edema led to death two hours following the introduction of iodopyracet (diodrast®) injected in the right side of the heart by means of an intracardiac catheter. These authors warned against the use of angiocardiography and believed that patients with arteriovenous fistulae are more susceptible to untoward cardiac effects because of the large amount of iodopyracet which may pass through the arteriovenous shunt into the left side of the heart and coronary vessels without adequate dilution in the pulmonary capillaries. Their patient, however, had had hypertension, arteriosclerosis, dyspnea and ankle edema, and previous episodes of transient numbness and muscular paralyses. Thirteen deaths following immediately upon the intravenous injection of contrast media for pyelography have been reported in the literature, and half of them were of patients with hypertension and cardiac decompensation.[15] Dotter[16] has surveyed centers doing angiocardi-

13. Wodehouse.[4] Baker, C., and Trounce, J. R.: Arteriovenous Aneurysms of the Lung, Brit. Heart J. **11**:409, 1949. Boerema, I., and Brilman, R. P.: Cavernous Hemangioma of the Right Lung, J. Thoracic Surg. **17**:705, 1948.

14. Sisson, J. H.; Murphy, G. E., and Newman, E. V.: Multiple Congenital Arteriovenous Aneurysms in the Pulmonary Circulation, Bull. Johns Hopkins Hosp. **76**:93, 1945.

15. Pendergrass, E. P.; Chamberlin, G. W.; Godfrey, E. W., and Burdick, E. D.: Survey of Deaths and Unfavorable Sequelae Following the Administration of Contrast Media, Am. J. Roentgenol. **48**:741, 1942.

16. Dotter, C. T., and Jackson, F. S.: Death Following Angiocardiography, Radiology **54**:527, 1950.

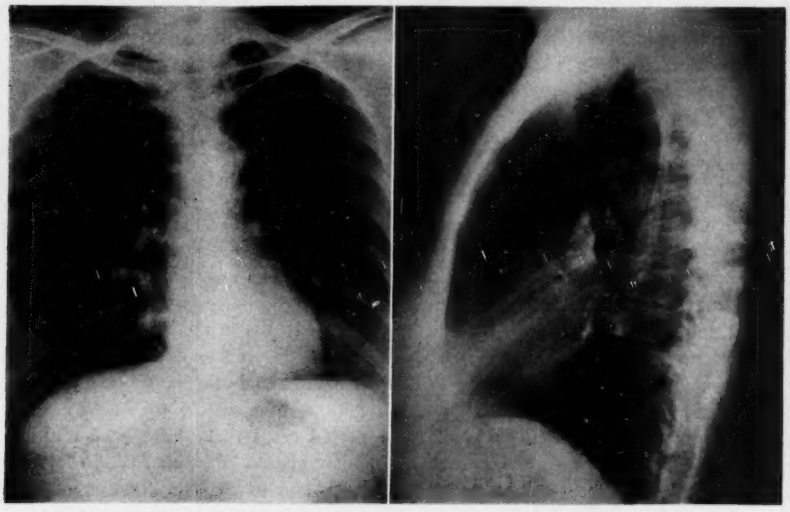

Fig. 9.—Conventional posteroanterior and lateral films, illustrating a small arteriovenous fistula just lateral to the left mid-cardiac segment and a few ill-defined opacities at the base of the left lung.

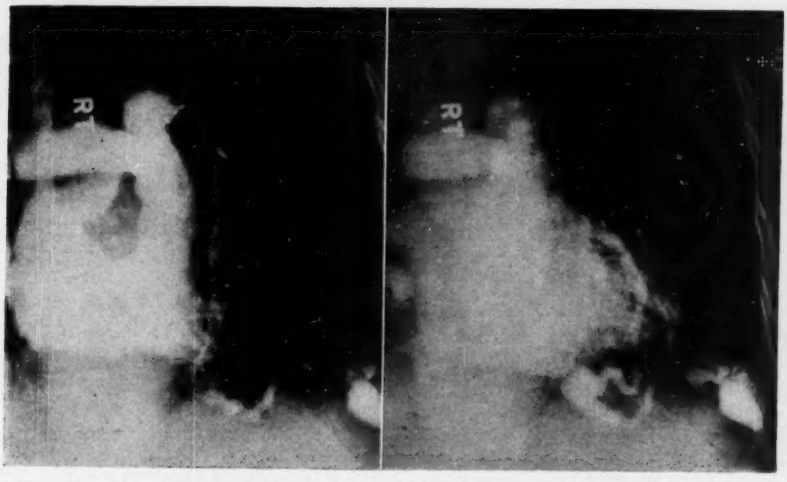

Fig. 10.—Angiocardiograms of the same patient as in Figure 9, showing the true extent and multiplicity of the vascular anomaly. The left picture was taken during the phase of arterial filling, while the right demonstrates some of the venous return.

ography in the United States, Canada, Great Britain, and Sweden and has collected reports of 26 deaths occurring in 6,824 examinations. The case reported by Sisson is the only one of death of a patient with a pulmonary arteriovenous fistula. Angiocardiography has been performed many times for arteriovenous fistula with no untoward results since Sisson's report of a fatal accident. However, it is felt that this procedure probably should not be carried out in patients with hypertension and/or cardiac failure.

With the use of conventional roentgenography and laminagraphy, we feel that a definitive diagnosis can be made without resorting to angiocardiography in a large majority of the cases, but that angiocardiography is warranted in every case in which surgical treatment is contemplated. Visualization of the pulmonary circulation and of the size and location of the involved vessels, as well as the identification of anomalous origins of the afferent artery or anomalous insertions of the efferent veins, may facilitate surgical treatment. Of more importance is the demonstration of multiple lesions which may have been overlooked in both the conventional films and the laminagraphic studies. Two cases in our series illustrated this possibility, since angiography demonstrated lesions which had been unsuspected (Figs. 9 and 10). Lesions at the base of the lung fields may be obscured by the diaphragm or by the cardiac shadow. In 60% of the reported cases there have been multiple lesions.[2c] The importance of bilateral involvement should be emphasized in relation to its effect upon the decision as to operability and in the conservation of lung tissue at the time of surgical treatment.

The suggestion of Lindskog and co-authors[5] that angiography be done on large (14 by 17 in. [35.6 by 43 cm.]) films in order to examine the entire lung field is pertinent, since in one examination which was done on 9 by 9 in. (22.9 by 22.9 cm.) roll film one of the lesions is shown on the edge of the film and might have been easily missed by a slight change in the position of the patient. However, there are advantages to serial filming whereby the afferent arteries and efferent venous drainage can be more accurately studied. Involvement of the chest wall by the pulmonary arteriovenous fistula is rare but has been reported.[17] This is important preoperative information for the surgeon.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pulmonary arteriovenous fistula is usually not difficult once the condition is suspected, although the pulmonary opacities have been frequently misinterpreted even when they were sufficiently characteristic to permit a correct diagnosis. When the fistulae are small, diagnosis may be more difficult, since their appearance may strongly resemble that of pulmonary metastases, primary lung tumors, benign cysts, tuberculomas, or bronchiectatic sacs filled with secretions. The important sign to recognize is the relation of the mass to the adjacent vessels. Proper evaluation of the tortuous bands connecting the parenchymal mass with the hilum is also important. Laminagraphy is usually quite successful in demonstrating the vascular continuity of the abnormal pulmonary shadow. Polycythemia vera can be differentiated by the presence of splenomegaly, leucocytosis, immature white cells in the peripheral blood, and a normal arterial blood oxygen content. The chest

17. Claggett, O. T., in discussion on Packard, G. B., and Waring, J. J.: Arteriovenous Fistula of the Lung, Arch. Surg. **56**:725 (June) 1948. Maier, H. C., in discussion on Lindskog and others.[5]

roentgenogram is usually of normal appearance in polycythemia vera, although Hirsch has described round pulmonary shadows; however, these are not vascular in nature and disappear after a short time.[18]

The presence of cyanosis, clubbed fingers, and a pulmonary murmur raises the possibility of congenital heart disease, but the presence of a normal cardiac silhouette is usually sufficient to exclude this possibility. One congenital abnormality which may give rise to some confusion is an aberrant insertion of a pulmonary vein, as described by Grishman, Poppel, and Simpson.[19] In this condition one of the pulmonary veins empties into the inferior vena cava and appears on the chest roentgenogram as a laterally convex vascular shadow running parallel to the lower right cardiac border. It is usually associated with a small interatrial septal defect with moderate dilatation of the pulmonary arteries and right ventricular enlargement. The characteristic location in the right lower medial lung field, the absence of a peripheral pulmonary mass, and the abnormal heart should serve to differentiate this condition. Pulmonary artery aneurysms are extremely rare and are usually found in the hilar region.[20] They are not associated with a parenchymal pulmonary mass contiguous with two or more vascular shadows. Lesions in the upper lobe may be mistaken for tuberculous infiltrates, as in one of our patients until continuity with hilar vessels was established by laminagraphy.

SUMMARY

Our roentgenographic experience with eight cases of pulmonary arteriovenous fistulae is reviewed for the purpose of determining the reliability of the diagnostic roentgen criteria for this condition. The role of fluoroscopic, laminagraphic, roentgen kymographic, and angiographic techniques is discussed. Conventional roentgenograms supplemented by laminagrams should lead to the correct diagnosis in most instances. Angiography is of great value in demonstrating multiple lesions not discovered by other techniques and is to be recommended before surgical treatment is instituted.

18. Hirsch, I. S.: Pulmonary Changes in Polycythemia Vera, Radiology **26**:469, 1936.

19. Grishman, A.; Poppel, M. H.; Simpson, R. S., and Susman, M. L.: The Roentgenographic and Angiocardiographic Aspects of (1) Aberrant Insertion of the Pulmonary Veins Associated with Interatrial Septal Defect and (2) Congenital Arteriovenous Aneurysm of the Lung, Am. J. Roentgenol. **62**:500, 1949.

20. Blades, B.; Ford, W., and Clark, P.: Pulmonary Artery Aneurysms, Circulation **2**:565, 1950.

LATE LYMPHATIC LEUKEMIA COMPLICATING HYPERSPLENIC SYNDROME

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WITH THE increased interest in hemolytic diseases, a large variety of disturbance in the circulating blood due to splenic dysfunction has been described. In the widest sense they result in cytopenias of various kinds associated with excessive blood cell destruction. The actual mechanism of destruction of red blood corpuscles is obscure, but the spleen seems to be involved in most instances. This mysterious organ of Galen is apparently not essential to life and health. Its relationship to the hemopoietic system has been noted from the changes in the blood following removal of the normal spleen [1]: Target cells, Howell-Jolly bodies, hypotonic fragility, leucocytosis, and diminished red cell destruction were found. The effects of the removal of the normal spleen are transitory and apparently harmless, whereas the pathological spleen in some cases may constitute a hazard to health and a danger to life unless it is removed.

The pathophysiology of the spleen may be manifested through inhibitory (hormonal) [2] or destructive mechanisms affecting any [3] or all [4] of the circulating blood elements. Dameshek speaks of hypersplenism as being of the "selective" and "total" types.[5] Doan [6] divides hypersplenism into primary and secondary.

From the Department of Medicine (Dr. Cochrane, director; Dr. Gross, resident), St. Vincent's Hospital.

1. Krumbhaar, E. B.: The Changes Produced in the Blood Picture by Removal of the Normal Mammalian Spleen, Am. J. M. Sc. **184**:215, 1932. Singer, K.; Miller, E. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, ibid. **202**:171, 1941. Lauda, E.: Die normale und pathologische Physiologie der Milz, Berlin, Urban & Schwarzenberg, 1933. Krumbhaar, E. B.: Functions of Spleen (Mysterii Plenum Organum) Galen, Physiol. Rev. **6**:160, 1926.

2. Ungar, G.: Endocrine Function of Spleen and Its Participation in Pituitary-Adrenal Response to Stress, Endocrinology **37**:329, 1945. Troland, C. E., and Lee, F. C.: Thrombocytopen: Substance in Extract from Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces Number of Blood Platelets, J. A. M. A. **111**:221 (July 16) 1938.

3. Wiseman, B. K., and Doan, C. A.: Primary Splenic Neutropenia: Newly Recognized Syndrome Closely Related to Congenital Hemolytic Icterus and Essential Thrombocytopenic Purpura, Ann. Int. Med. **16**:1097, 1942. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura, a Form of Hypersplenism, Blood **1**:27, 1946.

4. Doan, C. A., and Wright, C. S.: Primary Congenital and Secondary Acquired Splenic Panhematopenia, Blood **1**:10, 1946.

5. Dameshek, W., and Estren, S.: The Spleen and Hypersplenism, New York, Grune & Stratton, Inc., 1947.

6. Doan, C. A.: Hypersplenism, Bull. New York Acad. Med. **25**:625, 1949.

The primary form is understood as a hyperinstability of the spleen and may be sometimes inherited; the secondary hypersplenism is usually due to underlying diseases. Hypersplenism, in his opinion, is a hyperfunction of the spleen manifested by increased phagocytosis and sequestration of blood elements, with compensatory hyperplasia of bone marrow. Removal of the spleen will result in the disappearance or mitigation of symptoms.

The case reported below fulfills the diagnostic requirements of hypersplenism, but the final outcome of this splenectomy is unique and may serve as a contribution to further interpretation of the obscure mechanism of the spleen and the entire reticuloendothelial system.

REPORT OF A CASE

A 52-year-old white married woman was admitted to St. Vincent's Hospital for the first time on May 29, 1948. The chief complaints were weakness and tiredness for five to six weeks before admission to the hospital. Her family history, besides the fact that her brother had died from Hodgkin's disease, was not contributory. The patient had lived all her life in the state of New York. She had never been pregnant and gave no history of exposure to substances which might be toxic to the blood. The patient denied syphilitic infection.

Systemic review revealed that the patient was always in good health in the past. About five or six weeks prior to admission, she began to experience progressive weakness, fatigability, and shortness of breath on exertion. She also noted marked paleness of skin but did not give evidence of blood loss, or kidney or liver disease.

On admission the patient appeared not to be acutely ill. The head and neck were not remarkable. The skin and mucous membranes were pale, but there was no evidence of petechial hemorrhages. Peripheral lymph nodes were not felt. The tongue was smooth and pale. The lungs were clear. The heart size was within normal limits, and a Grade 2 soft systolic murmur heard best over the apex was present. The blood pressure was 115 mm. Hg systolic and 60 mm. Hg diastolic. Abdominal examination revealed the liver to be palpable just at the costal margin; the spleen was not felt. Vaginal and neurological examinations revealed no abnormalities.

Laboratory studies disclosed 4+ Mazzini, 4+ Kahn, and 3+ Kolmer reactions. The urine was normal. The blood picture revealed a hemoglobin concentration of 6 gm. and 3,200,000, red blood cells, with 2.7% reticulocytes. The white blood cell count was 5,600, with 67% neutrophiles, 32% lymphocytes, and 1% monocytes. The smear showed moderate anisocytosis and slight poikilocytosis. The corrected sedimentation rate was 0 mm. (Wintrobe method). The erythrocyte fragility determination revealed hemolysis in 0.52% saline solution with completion of hemolysis in 0.24% solution (nearly normal limits for this method). Hematocrit was 20%. The mean corpuscular volume was 86 cu. μ. Mean corpuscular hemoglobin was 26 γ. The mean corpuscular hemoglobin concentration was 20%. The thrombocyte count was 160,000 per cubic millimeter. The blood was Rh-positive, Type 1-0. Repeated peripheral blood examination after admission gave essentially the same result. Direct and indirect van den Bergh reactions were within normal limits. The icterus index was 8. Roentgen examination of chest and gastrointestinal tract failed to reveal definite lesions. One film suggested an enlarged spleen compressing the cardiac portion of the stomach. Fractional gastric analysis revealed absence of free hydrochloric acid, but 20 minutes after histamine injection free hydrochloric acid was present to the extent of 15 units. The stool was negative for occult blood.

The patient was in the hospital for 12 days and received 1,000 cc. of whole citrated blood. She refused to have a spinal or a bone marrow tap. On discharge the red blood cells were 2,600,000 per cubic millimeter; the hemoglobin concentration was 8 gm. per 100 cc., and the white blood cell count was 6,200.

After leaving the hospital, the patient was given three injections of 0.04 gm. of oxophenarsine (mapharsen®) hydrochloride, but further treatment with arsenicals was not given because of dermatitis. Then she received about 15,000,000 units of penicillin in 20 days. Her husband's blood had negative serologic reaction for syphilis. She also took vitamins and freshly made Blaud's pills (pills of carbonate of iron) and was doing well until September, 1948, when she was again hospitalized because of upper respiratory infection. At that time results of a routine urine examination were normal. The hemoglobin concentration was 12 gm.; the red blood cell

count was 4,200,000 and the white blood cell count 8,300, with a normal differential count. Mazzini and Kolmer reactions were negative. She remained well until February, 1949, when she again experienced tiredness and lack of usual energy and complained of cramps in the legs. She was readmitted to the hospital with signs of marked anemia and paleness. Physical examination gave essentially normal results, with the exception of the finding of a large, firm, nontender spleen which this time could be distinctly felt 3 fingerbreadths below the costal margin. There was no evidence of any peripheral lymph node enlargement, and the liver was felt just at the costal margin. Neurological examination revealed no abnormalities. Peripheral blood examination disclosed 6 gm. of hemoglobin, with a normal differential count. The blood smear revealed moderate anisocytosis and poikilocytosis. Thrombocytes were 150,000. Hematocrit was 26%. The coagulation time was 2½ minutes and the bleeding time 1½ minutes. The icterus index was 8. Direct and indirect van den Bergh reactions were within normal limits. The fragility test gave essentially the same results, as on first admission. Results of bone marrow examination were reported by Dr. M. Freund, pathologist, on March 4, 1949, as follows:

Cell	%	Cell	%	Cell	%
Myeloblasts	0.2	Nonsegmented forms	7.6	Erythroblasts	4.8
Promyelocytes	1.0	Segment neutrophiles	3.8	Normoblasts	68.0
Myelocytic neutrophiles	4.8	Segment eosinophiles	0.2	Plasmacytes	0.2
Myelocytic eosinophiles	2.0	Lymphoblasts	0.2	Megaloblasts	2.4
Metamyelocytes	1.8	Lymphocytes	3.0		
		Total nucleated cells 206,000			

The diagnosis was marked erythroblastic marrow showing megaloblastic elements.

Splenectomy was suggested, but the patient refused surgical treatment. Whole citrated blood, 2,500 cc., was given, and the patient left the hospital in slightly improved condition. After spending a week at home, she became so exhausted and weak that she was readmitted and was willing to submit to surgical treatment. On admission, the patient was icteric and the spleen was enlarged about 5 fingerbreadths below the costal margin. The physical examination gave essentially the same results as on previous admission.

Laboratory Data.—In the peripheral blood the red cell count was 1,930,000, with 3.4% reticulocytes. The white blood cell count was 2,400, with a normal differential count. The blood smear revealed moderate anisocytosis and poikilocytosis. Thrombocytes numbered 120,000 per cubic meter. Hematocrit was 8%. Urinalysis gave essentially normal results, with the exception of increased urobilinogen and a trace of albumin. The Mazzini and Kolmer reactions were negative. The icterus index was 15. The indirect van den Bergh reaction was 3.2 mg. per 100 cc. Urea was 27 mm. per 100 cc. During the next six days 4,500 cc. of whole citrated blood was given with reaction. The epinephrine test was performed on the eighth day of hospitalization. The peripheral blood picture before and after injection of epinephrine was as follows:

Time, A. M.	Red Blood Cell Count/Cu. Mm.	White Blood Cell Count/Cu. Mm.	Hemoglobin Concentration, Gm./100 Cc.
9:45	2,270,000	3,800	6.4
9:55	2,295,000	3,950	6.5
10:30	1 cc. of epinephrine (1:2,000) given hypodermically		
10:30	2,350,000	6,700	6.5
10:40	2,680,000	6,960	7
10:50	2,640,000	6,600	7
11:05	2,240,000	3,900	6.8

Further transfusions were attempted, but a severe reaction developed, and the patient became more jaundiced (icterus index, 26). Autoagglutinins and nucleated red cells were found in peripheral blood. About 1,000 cc. of washed cells was given with slight reaction. She was referred to surgery with a red blood cell count of 1,190,000, a white blood cell count of 3,800, and a hemoglobin concentration of 6 gm. Immediately after splenectomy, her red blood cell count rose to 2,900,000 and the white count to 13,800. At the time of discharge about 10 days after operation, the red blood count was 3,000,000 with a reticulocyte count of 5%. White blood cells were 6,900, with a normal differential count. Thrombocytes were 1,000,000 per cubic millimeter.

Pathological Study (Dr. M. Freund, May 23, 1949).—Gross Observations: The specimen was received in fresh condition; it consisted of a markedly enlarged spleen weighing 1,140 gm. The capsule was smooth and shiny throughout. The consistency was moderately soft. The organ had been previously incised over its convexity in the operating room. The splenic pulp was uniformly dark red and mottled by grayish-white, enlarged lymph follicles. The trabeculae were thin and were visible with the naked eye. The small blood vessels were congested. On serial section, occasional irregular hemorrhagic areas were seen. Near the hilum of the organ, several moderately soft, irregular, and enlarged lymph nodes were noted. They measured up to 3.5 cm. in diameter. On section they showed grayish parenchyma with numerous congested blood vessels.

Microscopic Diagnosis: Microscopic examination disclosed splenomegaly and diffuse replacement of the splenic pattern by nests of hematic cells of undifferentiated nature, as well as erythroblasts, myelocytes, and megakaryocytes. This histologic picture could be termed total myelosis of the spleen. There was also fibroblastic differentiation of the mesenchymal cells with the associated formation of collagen fibers. The lymph nodes showed lymphatic hyperplasia and erythrophagocytosis.

Further Clinical Course.—The patient was seen about six months later, in December, 1949. She was in good condition. The hemoglobin concentration was 12.2 gm., the red blood cell count, 4,800,000, hematocrit, 42%, and the white blood cell count, 9,500, with a normal differential count. The thrombocyte count was 290,000. The corrected sedimentation rate was 2 mm. She was seen again in February, 1950. The red cell count was 4,200,000, hematocrit 45%, and the white cell count 11,700. Results of physical examination were entirely normal.

The patient was readmitted to the hospital on Jan. 3, 1951, with the chief complaints of tiredness and crampy feeling in the legs for the last three weeks prior to admission. During the six months prior to admission, she had lost about 15 lb. (6.8 kg.), and she started to perspire heavily during the last two months. She also noted that her previously normal menstruation had become irregular and that she was spotting quite often. About one week prior to entry, she noted an enlarged node in the right side of the neck and had repeated nosebleeds. Physical examination gave essentially normal results, except for moderately enlarged peripheral lymph nodes in the neck, axillary, and inguinal regions. The lymph nodes were firm, discrete, freely movable, and not tender. There was a moderate paleness of skin and no evidence of mucosal hemorrhages.

Final Laboratory Findings.—The red blood cell count was 3,700,000, with 0.8% reticulocytes. The white blood cell count was 69,000, with 91% small lymphocytes, 3% lymphoblasts, 5% neutrophiles, and 1% eosinophiles. The hematocrit was 36%. The corrected sedimentation rate was 48 mm. in one hour. Results of urinalysis were not remarkable. The direct and indirect van den Bergh reactions were within normal limits. The Mazzini and Kolmer reactions were negative, as was the reaction to the Coombs test. A roentgenogram of the chest revealed no abnormalities. Results of biopsy of the neck node were reported on Jan. 4, 1951, by Dr. V. Kogan, pathologist, as follows:

The specimen was received in fixative and consisted of two well-encapsulated lymph nodes, one measuring 2 by 1 by 0.5 cm., the other measuring 1 by 0.5 by 0.5 cm. On section they were uniform in appearance and gray. Representative sections were taken for histologic examination. The histologic picture was consistent with the diagnosis of lymphatic leukemia or lymphosarcoma. Results of a bone marrow examination were reported on Jan. 3, 1951, by Dr. V. Kogan, as follows: Microscopically, the bone marrow was almost completely composed of cells of the lymphocytic series dilated with peripheral blood. The microscopic picture was compatible with the diagnosis of lymphatic leukemia.

COMMENT

This case presents several features which must be discussed before any conclusion may be drawn. The absence of spherocytosis, the normal fragility of red cells, the lack of familial history, and the absence of leucocytosis are against[7] the

7. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1942.

diagnosis of congenital hemolytic jaundice. The first two factors [8] and the absence of macrocytes [9] in the peripheral blood are against the diagnosis of acquired hemolytic anemia. The above diagnostic considerations, along with acholuric icterus, hyperplastic bone marrow, reticulocytosis, and anemia, manifested first by red cell destruction alone and then leading to pancytopenia, are characteristic of hypersplenism. However, the entire picture seems to be complicated by positive serologic reactions for syphilis.

Doan reports a case [6] in which syphilis precipitated hypersplenic crises. Dameshek [5] describes a case of tertiary syphilis in which pancytopenia developed, with cure by splenectomy. Also, acquired hemolytic anemia is reported in isolated cases of syphilis.[7] It is, however, well established that the symptomatic hemolytic anemia of infectious diseases disappears if the underlying disease is successfully treated.[8] Treatment of syphilis in the reported case remained without effect upon

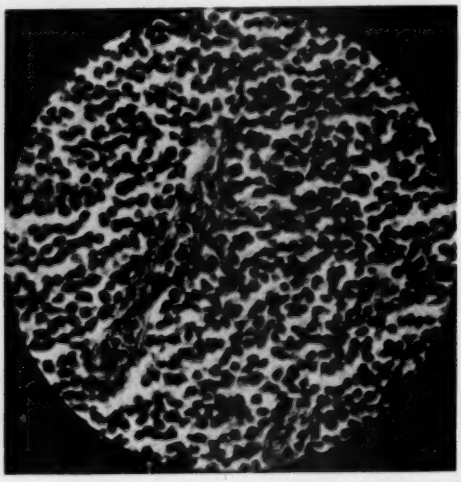

Fig. 1 (Jan. 4, 1951).—Lymph node (cervical), showing diffuse lymphocytic proliferation with loss of normal lymph node architecture. Eosin and hematoxylin stain; × 380.

the pathological behavior of the spleen. Splenectomy was followed by dramatic and complete recovery which lasted more than a year, until chronic lymphatic leukemia (Fig. 1) was discovered.

Doan [6] believes that failure of complete restoration of hematological equilibrium will happen only when hypersplenism is secondary to a constitutional disease involving other organs.

Haden [10] reports a case in which the diagnosis of idiopathic hemolytic anemia was assumed. After splenectomy, the hemolytic process showed continuation. Six months later lymphatic leukemia was diagnosed.

8. Singer, K., and Dameshek, W.: Symptomatic Hemolytic Anemia, Ann. Int. Med. **15**:544, 1941.

9. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in Series of 35 Cases, Ann. Int. Med. **12**:1782, 1939.

10. Haden, R. L.: Principles of Hematology, Philadelphia, Lea & Febiger, 1939.

On the other hand, cases of symptomatic hemolytic anemia [8] and thrombocytopenic purpura [6] in which Hodgkin's disease was demonstrated responded temporarily to splenectomy. Different types of leukemias and lymphosarcoma must be kept in mind in cases of hypersplenic syndrome. Against the latter diagnoses [11] in the reported case are the presence of hemolytic syndrome, the lack of enlargement of peripheral lymph nodes, the repeated normal sedimentation rate (until leukemia was discovered), and the results of bone marrow examination. The bone marrow findings and the microscopic examination of spleen showed no evidence of leukemic infiltration and did not fulfill the diagnostic criteria of the above-mentioned diseases. If one were to anticipate leukemia from microscopic appearance of the spleen and a hilar lymph node showing extramedullary blood cell formation (Figs. 2, 3, and 4) one would be inclined to suspect granulocytic [12] and not lymphatic leukemia. The microscopic section was reviewed by Dr. Paul

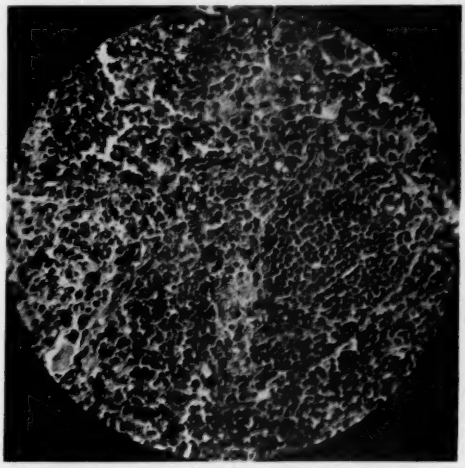

Fig. 2 (May 23, 1949).—Spleen: Area of extramedullary blood cell formation. In left lower field is a group of myelocytes mingled with dark, nucleated, smaller cells which are normoblasts. Two megakaryocytes (upper right and lower left corner). Eosin and hematoxylin stain; × 175.

Klemperer, of Mount Sinai Hospital, New York, and the above pathological reports and diagnoses were fully confirmed. This patient was treated on a few occasions with injections of oxophenarsine hydrochloride, which contained a benzene ring. Myeloid leukemia has been reported in persons exposed to benzene.[13] To our knowledge there is no case described in which lymphatic leukemia developed after syphilitic infection or antisyphilitic treatment with oxophenarsine.

11. Singer and Dameshek.[8] Dameshek, W., and Estren, S.: Hypersplenism, M. Clin. North America **34**:1271, 1950.

12. Dameshek, W.: Some Speculations on the Myeloproliferative Syndromes, Blood **6**:372, 1951.

13. Wintrobe.[7] Rawson, R.; Parker, F., Jr., and Jackson, H., Jr.: Industrial Solvents as Possible Etiologic Agents in Myeloid Metaplasia, Science **93**:541, 1941.

The above consideration should prove that underlying syphilitic infection and applied drugs had no influence on the leukemic complication in our case, and probably also that the hypersplenism was not secondary to syphilis. The relation

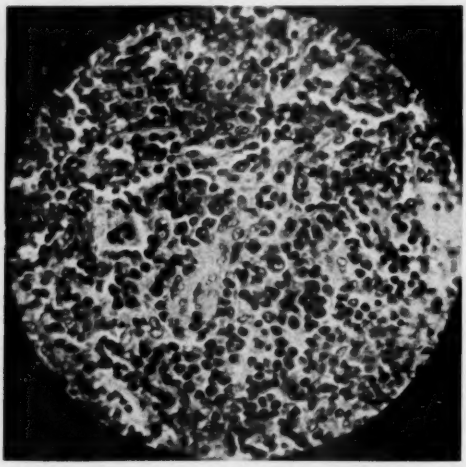

Fig. 3 (May 23, 1949).—Spleen: Another field, showing same extramedullary blood formation as in Figure 2. Eosin and hematoxylin stain; × 290.

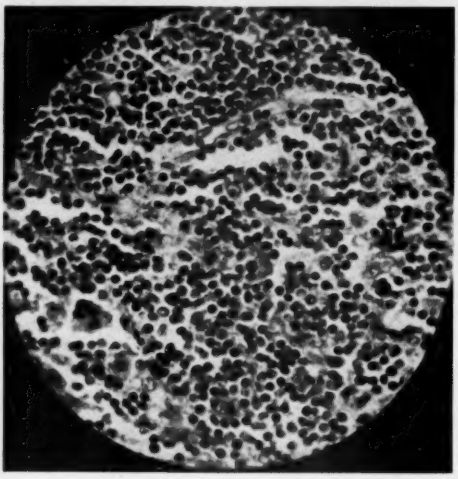

Fig. 4 (May 23, 1949).—Lymph node from splenic hilum, showing megakaryocytes. Eosin and hematoxylin stain; × 290.

between the two different pathological pictures of blood dyscrasia in the same patient remains obscure. However, the following factors and postulated theories may serve as a basis for bringing these two conditions to a common denominator:

First, the brother of the patient had had Hodgkin's disease. Warthin [14] believes that there is a genetic relation between Hodgkin's disease and leukemia. Herbut and his associates [15] assume that lymphoid or myeloid leukemia and Hodgkin's disease may arise from a common stem cell—the reticular cell. Apparently chemical substances and their ratio as found in urine by Miller and Turner,[16] have a specific stimulating effect upon the proliferation of myeloid or lymphoid cells, and also show relation to Hodgkin's disease. Secondly, lack of evidence of hemolytic anemia and the impalpable spleen at the time of onset of the disease, the inconclusive result of the epinephine test, and the presence of the megaloblastic element in bone marrow are in favor of a hormonal [17] mechanism of hypersplenism manifested in our case by maturation arrest.

Thus, one may assume that under the influence of an unknown stimulus there is increased hormonal activity of spleen, which in turn inhibits the bone marrow. If one realizes further that the spleen contains the body's largest single collection of reticuloendothelial cells, one has to accept that beneficial effect of removal of the spleen is associated with elimination of these cells. Splenectomy has not eliminated the primary stimulus which still acts upon the remaining, possibly genetically predisposed reticuloendothelial system, influencing the balance of acting substances [18] and leading finally to lymphoid metaplasia. This admittedly speculative conception correlates with Wiseman's [19] theory of the role of the reticuloendothelial system in the mechanism of production of leukemia. In view of the above consideration, the hypersplenic syndrome might be due also to impaired mechanism of the reticuloendothelial system.

SUMMARY

Functions of the normal and the pathological spleen are named. The hypersplenic syndrome is briefly discussed. A case is reported of a 52-year-old white woman with signs and symptoms of hypersplenism cured with splenectomy; one and a half years later the same patient displayed lymphatic leukemia. The results of extensive laboratory work-up and pathological observations are brought out in detail.

Differential diagnosis in the reported case is given. All possible predisposing factors leading to leukemia are discussed. An attempt was made to find a causative relationship between hypersplenism and leukemia.

Dr. P. Klemperer, Dr. M. Freund-Klemperer, and Dr. V. Kogan made diagnostic evaluations of pathological specimens.

14. Warthin, A. S.: Genetic Neoplastic Relationships of Hodgkin's Disease: Aleukaemic and Leukaemic Lymphoblastoma, and Mycosis Fungoides, Ann. Surg. **93**:153, 1931.

15. Herbut, P. A.; Miller, F. R., and Erf. L. A.: Relation of Hodgkin's Disease, Lymphosarcoma and Reticulum Cell Sarcoma, Am. J. Path. **21**:233, 1945.

16. Miller, F. R., and Turner, D. L.: Action of Specific Stimulators on the Hematopoietic System, Am. J. M. Sc. **206**:146, 1943.

17. Dameshek and Estren.[5] Palmer, J. G.; Kemp, I.; Cartwright, G. E., and Wintrobe, M. M.: Studies on the Effect of Splenectomy on the Total Leukocyte Count in the Albino Rat, Blood **6**:3, 1951.

18. Foster, C. G., and Miller, F. R.: Presence of Myelokentric and Lymphokentric Acid in Sera of Patients with Lymphomatoid Diseases, Proc. Soc. Exper. Biol. & Med. **75**:633, 1950.

19. Wiseman, B. K.: Is Leukemia a Disease of the Reticulo-Endothelial System? Blood **3**:867, 1948.

INFECTIONS WITH PSEUDOMONAS AERUGINOSA TREATED WITH POLYMYXIN B

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PSEUDOMONAS aeruginosa derived its earlier name, Bacillus pyocyaneus, from the blue-green pus of wounds from which it was cultured. It is one of about 30 related species of Gram-negative bacilli which are predominantly free-living in water and soil. Ps. aeruginosa is a normal inhabitant of the human intestinal tract, where it usually is present in small numbers and comes to the fore only when the normal coliform flora has been suppressed by antimicrobial drugs. This organism is not a pathogen in the usual sense of the word but may be called an "opportunist." It has no invasive powers and is ordinarily dealt with by the normal defenses of the body. Should these defenses not be developed, as in infants, or break down, as in debilitated persons, or should the bacillus be introduced passively into areas devoid of adequate natural defense mechanisms, it can set up an infection. Being closely related to entirely free-living organisms, Ps. aeruginosa has simple nutritional requirements and a broad enzyme spectrum, enabling it to synthesize its proteins from simple compounds. This makes interference with essential enzyme systems difficult and accounts, in part, for the resistance of this organism to most antimicrobial agents. Pseudomonas species also are known for their ability to adapt to unfavorable environments. They are consequently among the bacteria most readily acquiring resistance to antimicrobial drugs. These features have made difficult the management of Pseudomonas infections.[1]

Ps. aeruginosa is found not infrequently on skin surfaces and occasionally in the air. From these sources it contaminates surface wounds, burns, debilitated mucous membranes, drugs, and medical instruments. Through contaminated equipment or solutions, Pseudomonas may be introduced into the urinary tract in the course of instrumentation, into the meninges during lumbar puncture or induction of spinal anesthesia, or into surgical wounds during dressings. These infections are indolent, often evoking little systemic response, but they are stubborn, and occasionally dissemination and sepsis occur. In mixed infections with other organisms, Ps. aeruginosa contributes to the chronicity of the process and prevents healing. It reaches the blood stream not by active spreading invasion but usually

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This study was aided by a grant from Burroughs Wellcome & Company, Inc., Tuckahoe 7, N. Y., which issues polymyxin B as aerosporin.® Supplies of this brand of polymyxin B sulfate were generously made available by Dr. D. S. Searle, of Burroughs Wellcome & Company, Inc.

1. Stanley, M. M.: Bacillus Pyocaneus Infections: Review Report of Cases and Discussion of Newer Therapy Including Streptomycin, Am. J. Med. **2**:253-277; 347-367, 1947.

through massive seeding from a focus and results in sepsis only when a debilitated patient has lost most antibacterial defenses.

In such circumstances Ps. aeruginosa may be a true pathogen. Chemotherapy of processes due to this etiological agent has been notoriously difficult. While sulfonamide, streptomycin,[2] and aureomycin [3] therapy has occasionally suppressed the organisms sufficiently to permit natural body defenses to gain the upper hand, most strains of Ps. aeruginosa have recently been resistant to these drugs in vitro.[4] The antimicrobial agent most active against this organism is polymyxin.[5]

The polymyxins are a group of stable basic polypeptides isolated from Bacillus polymyxa.[6] Depending on their amino acid composition, they have been given designating letters A, B, C, D, and E. Earlier studies with polymyxin D [7] had indicated a significant degree of nephrotoxicity which interfered with its clinical usefulness.[8] Recently, purified preparations of polymyxin B have become available for hospital use. We have used polymyxin B sulfate for more than two years in treatment of 35 selected patients with Pseudomonas infections. This paper describes the clinical usefulness of this agent through illustrative case presentations and reports on its safety with respect to renal toxicity.

REPORT OF CASES [9]

The Pseudomonas infections treated with polymyxin B are summarized in Table 1. The following cases illustrate the prominent problems:

CASE 1.—*Acute Pyelonephritis Due to Ps. Aeruginosa* (Chart 1).

C. H., a 14-month-old girl, entered the hospital on May 30, 1951. Birth and early development of the child had not been remarkable except for several recurrent episodes of fever since July, 1950, attributed to urinary tract infection. Detailed urological study had revealed a congenital stricture of the bladder neck, without other abnormalities. Renal function was entirely normal. The child was hospitalized in order that an attempt might be made to obtain surgical relief of this obstruction. Examination on admission revealed a thin but well-developed girl,

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2. Weinstein, L., and Perrin, T. S.: Meningitis Due to Pseudomonas Pyocyanea: A Report of 3 Cases Treated Successfully with Streptomycin and Sulfadiazine, Arch. Int. Med. **29**:103-111 (July) 1948. Bedell, H., and Paley, S. Ş.: Recurrent Pseudomonas Pyocyaneus Meningitis Following a Gram Positive Meningitis, New York J. Med. **51**:1431-1432, 1951.

3. Neter, E.; Krauss, R. F.; Egan, G. J., and Mason, T. H.: Aureomycin Treatment of Meningitis Due to Bacillus Pyocyaneus and Bacillus Aerogenes: Report of 2 Cases with Recovery, J. A. M. A. **142**:1335-1337 (April 29) 1950.

4. (*a*) Frank, P. F.; Wilcox, C., and Finland, M.: In Vitro Sensitivity of Bacillus Proteus and Pseudomonas Aeruginosa to 7 Antibiotics, J. Lab & Clin. Med. **35**:205-214, 1950. (*b*) Jackson, D. M.; Lowbury, E. J. L., and Topley, E.: Pseudomonas Pyocyanea in Burns: Its Role as a Pathogen and the Value of Local Polymyxin Therapy, Lancet **2**:137-147, 1951.

5. (*a*) Footnote 4. (*b*) Pulaski, E. J.; Baker, H. J.; Rosenberg, M. L., and Connell, J. F.: Laboratory and Clinical Studies of Polymyxin B and E, J. Clin. Invest. **28**:1028-1031, 1949. (*c*) Jawetz, E., and Coleman, V. R.: Laboratory and Clinical Observations on Aerosporin (Polymyxin B), J. Lab. & Clin. Med. **34**:751-760, 1949.

6. Stansly, P. G.: The Polymyxins: Review and Assessment, Am. J. Med. **7**:807-818, 1949.

7. Schoenbach, E. B.; Bryer, M. S.; Bliss, E. A., and Long, P. H.: Polymyxin: A Note on Experimental and Clinical Investigation, J. A. M. A. **136**:1096-1098 (April 24) 1948.

8. Schoenbach, E. B.: The Newer Antibiotics: Polymyxin, Chloromycetin, and Aureomycin (Janeway Memorial Lecture), Mt. Sinai Hospital **16**:71-108, 1949.

9. Dr. John A. Anderson, Dr. Harold Faber, Dr. F. Hinman Jr., Dr. J. Hopper, and others permitted treatment of their patients.

without any significant positive findings. Laboratory examinations revealed a hemoglobin concentration of 13 gm. per 100 ml. and a white blood cell count of 10,000 per cubic millimeter, with 11% lymphocytes. The serum creatinine was 0.9 mg. per 100 ml. The urine was clear and neutral and contained no sugar, protein, or acetone and only occasional white blood cells and epithelial cells.

A transurethral resection was performed on May 31, and an indwelling catheter was put in place. On the second postoperative day the child displayed irritability, anorexia, and fever.

TABLE 1.—*Patients with Infections Due to Ps. Aeruginosa Treated with Polymyxin B*

Type of Infection	No. of Patients	Polymyxin B: Route and Dose	Result of Treatment
Pyelonephritis, acute	4	1.5-2.8 mg./kg./day intramuscularly for 6-8 days	Permanent cure in all patients
Pyelonephritis, chronic	8	1.5-2.5 mg./kg./day intramuscularly for 6-11 days	Temporary suppression of organisms with improvement; later relapse in all
Meningitis	2	5 mg. intrathecally daily 4 times then every 2 days for 2-3 wk.	Permanent cure without sequelae in 1; in other cerebrospinal fluid sterilized but late hydrocephalus developed; treatment begun too late
Arthritis, purulent	1	10 ml. daily of solution of 1 mg./ml. injected into joint for 5 days	Eradication of organisms in 6 days
Conjunctivitis	2	Solution of 1 mg./ml. instilled 4 times a day for 5 days	Discharge stopped; organisms eradicated
Otitis media, chronic	5	Solution of 1 mg./ml. instilled 4 times a day for 6 days	Discharge stopped; organisms eradicated
Sinus tract, infected	3	Solution of 1 mg./ml. instilled 3 times a day for 5-10 days	Organisms eradicated and sinus healing in 2; in 3d superinfection with Proteus vulgaris
Sinusitis, maxillary, chronic	1	Irrigation with solution of 0.5 mg./ml. daily for 7 days	Discharge diminished; organisms eradicated
Wound infection	9	Solution of 1 mg./ml. applied topically (continuous wet dressings) and instilled into wound for 4-10 days	Discharge stopped; organisms eradicated and prompt healing of wound in 8; one not affected

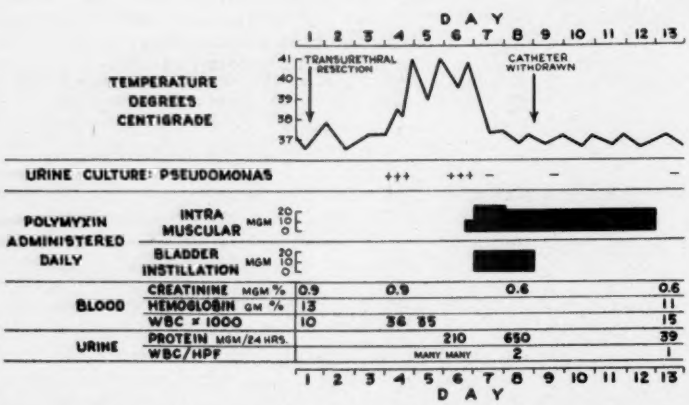

Chart 1.—Coure of infection with Ps. aeruginosa and results of polymyxin B therapy in Patient C. H., 14 months old, weighing 20 lb. (9.1 kg.), with congenital stricture of bladder neck and postoperative pyelonephritis.

The next day she presented the picture of sepsis, with high fever, emesis, and a white blood cell count of 36,000, with 82% polymorphonuclear leucocytes. A single blood culture was negative for pathogens. The urine was loaded with pus cells and contained some protein. Urine culture revealed large numbers of Ps. aeruginosa organisms, resistant in vitro to all available chemotherapeutic agents but inhibited completely by 0.5 γ per milliliter of polymyxin B. This drug was, therefore, administered both intramuscularly (25 mg. per day; later 20 mg. per day)

and through an indwelling catheter into the bladder (20 mg. daily). There was prompt clinical response; the temperature returned to normal; emesis stopped; pus and protein disappeared from the urine; the urine culture became sterile and remained so, even after the catheter had been withdrawn and polymyxin B administration discontinued. A total of 150 mg. of polymyxin B was injected intramuscularly in six days, without any symptoms or laboratory evidence of toxic effects. Follow-up examinations four months later indicated complete and lasting recovery.

Comment.—It is uncertain whether Ps. aeruginosa was present in the urinary tract above the obstruction, or whether it was introduced at the time of surgical treatment. There can be little doubt, however, that the prompt use of polymyxin B prevented chronic renal infection and may have been lifesaving. While no positive blood culture was obtained for this child, similar patients with proved bacteremia have responded equally well.[10] The data given in the chart likewise illustrate that parenteral administration of 2.2 to 2.8 mg. of polymyxin B per kilogram of body weight per day for six days produced no renal damage whatsoever. Such dramatic therapeutic response is the rule in acute Pseudomonas pyelonephritis treated with polymyxin B.[11] Chronic pyelonephritis may temporarily respond, but we have not succeeded in eradicating the infecting organism with the use of this drug or any other agent.

CASE 2.—*Meningitis Due to Ps. Aeruginosa* (Chart 2).

A. G., a 2½-year-old girl, was hit by an automobile on Oct. 8, 1950, sustaining multiple lacerations of the head and face, avulsions of the scalp heavily contaminated with dirt and sand, and skull fractures involving the left zygoma, the right side of the mandible, and the left maxillary sinus. There were also a pneumothorax and several fractured ribs. After initial treatment for shock, antitoxin was administered, the wounds were cleansed, and continuous wet dressings applied. Penicillin and aureomycin were given in large doses for three weeks. On Nov. 2, burr holes were made in the outer table of the skull to promote formation of granulation tissue for future skin grafts. During surgical manipulation some cerebrospinal fluid escaped into the wound. On the first postoperative day there was a temperature elevation to 39.3 C. (102.7 F.), but no physical signs of meningitis were present. The white blood cell count on Nov. 3 was 11,300, with normal distribution. On treatment with aureomycin, 750 mg. daily by mouth, there was slight improvement, although a spiking fever persisted. On the fifth postoperative day stiffness of the neck was first detected, and culture of the wound revealed a predominance of Ps. aeruginosa. The white blood cell count on Nov. 8 had risen to 24,400, with 80% polymorphonuclear leucocytes; examination of the spinal fluid yielded 1,750 cells, but only slightly elevated protein and essentially normal sugar levels. The spinal fluid culture grew Ps. aeruginosa. Growth persisted on cultures in spite of parenteral treatment with penicillin, streptomycin, and sulfadiazine. A single intrathecal dose of 25 mg. of streptomycin was followed by transient paralysis and shock. The Pseudomonas organism was highly resistant to all usual chemotherapeutic drugs in vitro but was completely inhibited by 0.5 γ per milliliter of polymyxin B. This drug was, therefore, administered intrathecally in a dose of 5 mg. daily for four days and then every other day. The clinical response was dramatic and immediate, and spinal fluid cultures became negative. Roentgenograms of the skull on Nov. 17 revealed osteomyelitis of the roof of the left orbit. When polymyxin administration was discontinued on Nov. 23, a relapse of the meningitis occurred. There were again high fever, stiffness of the neck, and positive spinal fluid culture (Ps. aeruginosa), with pleocytosis, presumably from dissemination of the infection from the area of osteomyelitis. Polymyxin B was, therefore, injected intrathecally, 5 mg. daily for three days, then every second or third day for four weeks. Again there was prompt response of clinical signs and laboratory findings. The child gained weight; the wounds healed well, and the osteomyelitis localized satisfactorily and eventually

10. Jawetz, E., and Marshall, M. S.: Role of the Laboratory in Antibiotic Therapy, J. Pediat. **37**:545-554, 1950.

11. Pulaski and others.[6b] Jawetz and Marshall.[10]

healed. Polymyxin B therapy was discontinued on Dec. 23, 1950, when the cell count and protein and sugar levels of the spinal fluid had virtually returned to normal. During this long course of intrathecal administration of polymyxin B, no sign of toxicity developed under close observation. Levels of 0.5 to 5 γ of polymyxin B per milliliter were present in the spinal fluid for 24 to 36 hours after each injection, but there was no apparent accumulation of the drug. The urine and the serum creatinine value were normal on many determinations. The child continued to make an uneventful recovery, without any sequelae, and, when examined six months later, was entirely well.

Comment.—The failure of other drugs to control the meningeal infection suggests that polymyxin B saved this child's life. The relapse following the first short course of therapy with the drug indicates that it had suppressed the infection in the meninges but failed to kill the Ps. aeruginosa in the area of osteomyelitis. This was accomplished by the second, prolonged course, resulting in complete recovery

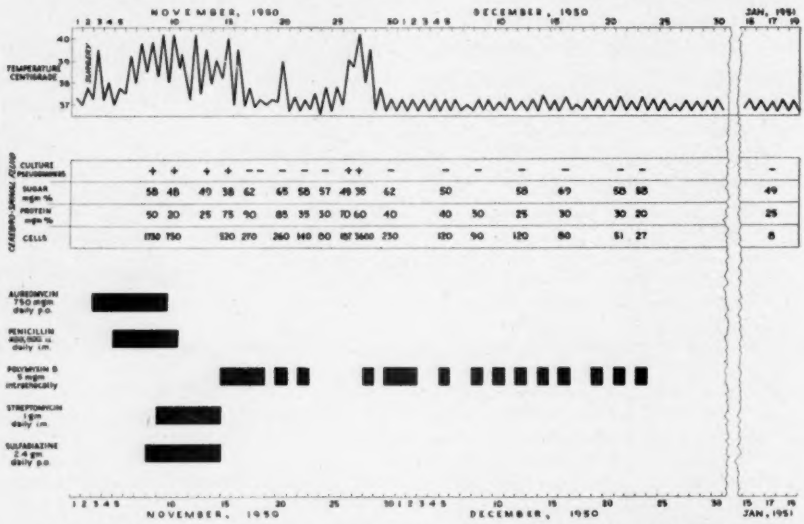

Chart 2.—Course of infection with Ps. aeruginosa and results of chemotherapy in Patient A. G., aged 2½ years, with Pseudomonas meningitis following an automobile accident and surgical treatment.

without sequelae. It is particularly noteworthy that intrathecal administration of the drug did not produce noticeable irritation.

A number of reports testify to the efficacy of polymyxin B therapy in Pseudomonas meningitis.[12] It should be pointed out particularly that in meningitis intrathecal therapy with polymyxin B is essential (the drug does not penetrate from the systemic circulation into the meninges) and that in the absence of other systemic foci of infection with Ps. aeruginosa polymyxin probably need not be administered intramuscularly.

12. (*a*) Schoenbach.[8] (*b*) Hayes, E. R., and Yow, E.: Meningitis Due to Pseudomonas Aeruginosa Treated with Polymyxin B, Am. J. M. Sc. **220**:633-637, 1950. (*c*) Tomlin, C. E.: Pseudomonas Meningitis: Report of a Case with Recovery After Polymyxin B Therapy, A. M. A. Arch. Int. Med. **87**:863-867 (June) 1951.

CASE 3.—*Wound Infection with Ps. Aeruginosa.*

B. S., a 36-year-old housewife, had suffered from chronic right atrophic pyelonephritis for a number of years. Studies with iodopyracet injection (diodrast®) revealed the left kidney to be essentially normal, but there was virtually no excretion of the dye on the right. Left kidney function was good, but no phenolsufonphthalein was excreted from the right. As there had been some recurrent rise in blood pressure, right nephrectomy was performed on June 16, 1951, with removal of a contracted, atrophic kidney. Postoperatively the patient received terramycin, 2 gm. daily by mouth. On the third postoperative day a greenish discharge was observed on the dressings, and a culture from the wound revealed Ps. aeruginosa. Sensitivity tests indicated complete resistance to all usual antimicrobial drugs but complete inhibition by 1 γ of polymyxin B per milliliter. While these studies were in progress, the patient received streptomycin, 2 gm. daily intramuscularly, sulfadiazine in full doses by mouth, and continuous wet dressings to the wound. The greenish discharge increased in amount with this regimen, and the patient exhibited an elevation in temperature to 38.1 C. (100.4 F.). On June 23 polyethylene tubing was inserted in three places into the incision, and irrigation was carried out four times daily with 20 ml. of a solution containing 1 mg. of polymyxin B per milliliter of sterile saline solution. In addition, dressings soaked in the same solution were applied. The fever and the discharge promptly disappeared, and on June 28 cultures from the wound were sterile. Irrigations were discontinued the next day, and subsequently the wound healed rapidly and completely.

Comment.—Other drugs have been used in controlling surface infections with Ps. aeruginosa [13] with more or less success. The outstanding characteristics of polymyxin B solutions employed for this purpose are the rapidity with which they kill the organisms and permit healing and their lack of irritation to the tissues. Thus, solutions of polymyxin B (0.5 to 1.0 mg. per milliliter) appear preferable to 2-phenoxy ethanol ("phenoxetol"), sulfonamides, various acridine derivatives, or sodium propionate for topical application. An extensive study on the prevention and treatment of Ps. aeruginosa infection of burns also indicated the great value of topical polymyxin application [4b] and emphasized the safety of this treatment.

CASE 4.—*Asthma with Chronic Sinus Infection, Due to Ps. Aeruginosa.*

E. B. M., a 54-year-old laboratory technologist, entered the hospital on July 18, 1951, complaining of intractable asthma for four weeks. The patient had suffered from attacks of asthma for many years but had enjoyed some periods of excellent health lasting up to four years. During her asthmatic periods she had received large amounts of epinephrine, aminophylline, oxygen, and various expectorants, with little relief. On two occasions she had entered true status asthmaticus, with prolonged unconsciousness. Her attacks had been relieved by administration of large amounts of antibiotics in the past. She had consumed considerable quantities of all known antimicrobial agents and had also undergone a Caldwell-Luc operation in 1950 to establish drainage of her infected sinuses. Cultures of material from the sinuses had on many occasions since 1949 revealed a pure growth of Ps. aeruginosa. She had raised purulent sputum in amounts up to 50 ml. daily. While she was believed to be allergic to a variety of inhalants and foods, no clear-cut relationship had been established between her attacks and a specific hypersensitivity.

Physical examination on entry revealed an obese, perspiring woman wheezing and coughing constantly. The temperature was 37.4 C. (99.3 F.), the pulse rate 74, and the blood pressure 140/80. The outstanding positive physical findings were profuse postnasal drainage and increased resonance of the lungs, with many squeaks, expiratory wheezes, and musical rales. The heart and abdomen were not remarkable. Roentgen examination indicated marked clouding of the maxillary sinuses but essentially normal lung fields. An electrocardiogram was not remarkable. Laboratory examinations showed 16.5 gm. of hemoglobin per 100 ml. and a white

13. Theodore, F. H.: Use of Sodium Propionate in External Infections of the Eyes, J. A. M. A. **143**:226-228 (May 20) 1950. Stanley.[1] Jackson and others.[4b]

blood cell count of 8,500, with 7% eosinophiles, but otherwise normal distribution. The packed red cell volume was 49%, and the corrected erythrocyte sedimentation rate, 27 mm. per hour. The urine was essentially normal. Cultures from sinus washings and sputum indicated a predominance of Ps. aeruginosa and also Streptococcus viridans and Neisseria. The Pseudomonas organisms were inhibited by 1 γ per milliliter of polymyxin B but were entirely resistant to other drugs in vitro.

The patient required oxygen in addition to frequent injections of epinephrine and aminophylline. She also received polymyxin, 150 mg. daily by intramuscular injections (2.5 mg. per kilogram of body weight per day) for 13 days, and her maxillary sinuses were irrigated daily for seven days with about 20 ml. of a solution containing 0.5 mg. of polymyxin per milliliter of saline solution. The patient tolerated the drug well, but there was no improvement for several days. On the eighth day of polymyxin therapy, Pseudomonas organisms could, for the first time, not be cultured from material from the maxillary sinuses or sputum. The next day her asthma ceased rather abruptly. Follow-up cultures for three weeks indicated a continued absence of Pseudomonas organisms and an essentially normal flora in the respiratory tract.

A short course of treatment with corticotropin (320 mg. in five days) was given subsequently without noticeable effect. Seven weeks later the patient had an infection of the upper respiratory tract, with recurrence of asthma and with reappearance of Ps. aeruginosa in the sinus secretions. Combined local and systemic treatment with polymyxin B again resulted in apparent removal of this organism.

Comment.—It is not implied that Pseudomonas infection was principally responsible for the severe asthma in this patient. It is notable, however, that combined topical and systemic administration of polymyxin B resulted in apparent eradication of this organism and simultaneous relief from the asthma. The lethal action of polymyxin B on Ps. aeruginosa is especially useful in treatment of chronically infected mucous membranes. Equally satisfactory results have been observed in infections of the middle ear and of the conjunctiva treated with topical applications of solutions of polymyxin B containing 0.5 to 1.0 mg. per milliliter. No local sensitization has been encountered.

SAFETY OF THE DRUG

So little polymyxin B is absorbed from mucous membranes or wounds as to make even prolonged topical administration quite safe.[4b] With parenteral injection, however, the question of potential renal toxicity is of great importance, especially in treatment of relatively benign conditions. In a number of publications [14] reference is made to the "nephrotoxicity" of polymyxins, without specifying the purity of preparations used. In the present study renal function was, therefore, carefully checked in patients receiving polymyxin B parenterally. In addition to routine urinalyses, measurements were made of urinary protein excretion, blood nonprotein nitrogen, serum creatinine, creatinine clearance, phenolsulfonphthalein excretion, and Addis counts, at frequent intervals. Among 28 patients treated for seven days with daily intramuscular doses of 1.5 to 2.8 mg. per kilogram of body weight, there was a slight and transient increase in proteinuria in 7 persons and a significant increase in the number of white and epithelial cells (Addis count) in 3. These changes regressed in a few days after discontinuance of therapy. No other abnormalities were encountered, but, on the contrary, there were four instances in which an originally elevated serum creatinine or blood nonprotein nitrogen level returned to normal during therapy.

14. Stansly.[6] Schoenbach.[7, 8] Tomlin.[12c]

Detailed studies of renal function were also performed on three patients treated with daily intramuscular doses of 1.5 to 2.5 mg. per kilogram of body weight for 13 days. The summary of pertinent findings (Table 2) indicates that the preparation of polymyxin B employed (purity, 75%) was devoid of serious nephrotoxicity.

Other side-actions encountered in this study consisted of irritation at the site of injection, requiring the admixture of procaine to prevent local pain, and neurotoxic symptoms of varying intensity. The latter consisted of circumoral and peripheral paresthesias, moderate dizziness, and a feeling of weakness without objective signs.[5c] All neurotoxic symptoms disappeared within 24 to 48 hours after discontinuance of polymyxin B injections. Their intensity varied greatly in different patients and to some extent with different lots of the same drug and was not strictly proportional to the amount of drug injected. These findings agree with the observations reported by Kagan.[15]

COMMENT

Ps. aeruginosa is an inhabitant of the human intestinal tract and is commonly found on the skin. It is not an invasive pathogen, but when introduced into wounds

TABLE 2.—*Studies of Renal Function in Patients Receiving Prolonged Courses of Therapy with Polymyxin B*

	Patient V. R. (1.5 Mg./Kg./Day Polymyxin B for 13 Days)					Patient E. C. (1.8 Mg./Kg./Day Polymyxin B for 13 Days)					Patient E. B. M. (2.5 Mg./Kg./Day Polymyxin B for 13 Days)			
	Pre-treatment	Day of Treatment			Post treatment	Pre-treatment	Day of Treatment			Post-treatment	Pre-treatment	Treatment		Post-treatment
		4th	8th	12th			4th	7th	11th			4th	9th	
Blood nonprotein nitrogen, mg./100 ml.	28	30	26	24	27	22	25	29	30	20	40	29	35	32
Serum creatinine, mg./100 ml.	0.9	0.8	1.0	0.7	0.8	0.9	1.1	0.6	1.0	1.0	0.7	0.9	1.0	1.0
Corrected creatinine clearance, ml./min.	86.3	100.4	78.8	92.0	85.5	76.8	78.7	131.0	100.0	81.1	88.8	77.2	108.7	72.1
Phenolsulphonphthalein excretion, % (two hr.)	85	75	80	75	80	75	65	75	80	80	80	..	75	90
Addis count:														
Protein, gm./24 hr.	0	0	0.2	0.1	0	0	0	0	..	0	0.3	2.0	0	0
Casts × 1,000/24 hr.	0	0	0	0	0	0	0	0	..	0	0	100	100	25
R.B.C. × million/24 hr.	2.4	4.1	4.6	2.0	2.8	16.6	19	9.5	..	10	1.2	2.5	0.4	0.5
W.B.C. × million/24 hr.	31.0	14.3	4.8	11.3	7.0	64.6	35	84	..	52	3.7	14.5	3.0	2.3

or closed systems, such as the urinary tract or the subarachnoid space, it may result in progressive disease. This organism is more versatile than most other Gram-negative bacteria (with the exception of Proteus) and is but little affected by most available chemotherapeutic agents.

While the majority of infections with Ps. aeruginosa are not fatal, they tend to be chronic and disabling. It is fortunate, therefore, that many strains of this organism are exceedingly sensitive to polymyxin B, being inhibited in vitro by 0.1 to 5 γ per milliliter [16] and killed by two to five times greater concentrations. Such concentrations are readily accomplished by the administration of amounts of the drug which do not produce significant toxic effects. For topical application much higher concentrations of polymyxin B permit the rapid eradication of most strains of Ps. aeruginosa without irritation to delicate tissues, mucous membranes, or granulating surfaces. Absorption from such areas is negligible.

15. Kagan, B. M.; Krevsky, D.; Milzer, A., and Locke, M.: Polymyxin B and Polymyxin E, J. Lab. & Clin. Med. **37**:402-414, 1951.

16. Frank and others.[4a] Kagan.[15]

Polymyxin B does not permit readily the development of resistance in populations of micro-organisms exposed to its action.[5c] In the present series, "escape" of bacteria from the suppressive action of the drug was observed only once. This occurred in an elderly man with chronic pyelonephritis due to Ps. aeruginosa. From the third to the eighth days of his therapy with 2.1 mg. of polymyxin B per kilogram of body weight per day administered intramuscularly, Pseudomonas could not be cultured from the urine. On the ninth day, however, the bacteria reappeared in large numbers and proved to be resistant to 50 γ per milliliter of polymyxin B in vitro.

Polymyxin B exerts its most beneficial activity, not in diffuse tissue infections, but in processes localized on surfaces or within closed systems. While polymyxin B has no place in the treatment of infections such as typhoid or brucellosis, in spite of the in vitro sensitivity of the organisms, it is well suited to therapy of the type of infections encountered with Ps. aeruginosa. With the apparent increasing frequency of infections with this organism, attributable to cross contamination in hospitals,[17] polymyxin B should fill a real need in clinical practice.

It has been the experience in a number of hospitals that Ps. aeruginosa establishes itself as a secondary invader of burns, wounds, and discharging ears and becomes a common cause of urinary tract infections.[18] This must be attributed in part, at least, to the widespread and somewhat indiscriminate use of antibiotics. These invaluable drugs suppress many members of the normal flora of the human body, effecting marked distortion of bacterial populations. As the more susceptible bacteria are suppressed, they are replaced by the more resistant varieties of microorganisms. Thus, not only do Proteus, Pseudomonas, certain staphylococci, and yeasts increase greatly in numbers in the individual patient, but their prevalence also arises in the community. This type of alteration in microflora is particularly striking in hospital populations, where cross contamination is more frequent and resulting infection more closely observed. No remedy can be suggested for this trend, except to urge the judicious use of antibiotics and their administration only when properly indicated. In cases in which Ps. aeruginosa infections arise, treatment with polymyxin B will be helpful and frequently curative.

SUMMARY

Pseudomonas aeruginosa is not a common pathogen but behaves as an "opportunist," causing true infections only under certain conditions of impaired host resistance.

Thirty-five selected patients with Ps. aeruginosa infection have been treated with polymyxin B, with good results. This drug not only is the most active agent available at present for the treatment of Pseudomonas infections but also appears to be quite safe for topical and parenteral administration in dosage schedules suitable for eradication of the infection in most instances.

17. Hospital Infection, editorial, Lancet **1**:1310-1311, 1951.

18. Footnote 17. Jackson and others.[4b]

PROBLEMS OF CATION-EXCHANGE-RESIN THERAPY

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RESTRICTION of sodium intake in the form of a salt-poor diet has become an accepted form of therapy for various disease entities. These include particularly congestive heart failure, attacks of pulmonary edema, the nephrotic syndrome, and hepatic disease with ascites.

It is no easy task to prepare a varied and palatable diet which contains only 1 to 2 gm. of sodium chloride. Few patients will tolerate the monotonous, tasteless low-sodium diet for more than brief intervals. Any means which would permit these patients to ingest a diet containing a reasonable amount of sodium chloride, and yet enable them to excrete the ingested sodium without difficulty, would be a welcome solution to this problem. The use of cation-exchange resins has been suggested as a method of accomplishing this.

In 1946 Dock fed a hydrogen-cation exchanger to rats to obtain sodium depletion.[1] In 1947 Gilwood suggested the use of an ammonium exchanger for this purpose.[2] Greenblatt and Gilwood in 1948 reported the use of an ammonium sulfonated polystyrene-type ion exchanger (permutit® Z, WIN 3000) in the treatment of congestive heart failure.[3] This exchanger has the ability of combining with the cations (sodium, potassium, calcium, magnesium) of the diet and digestive juices while in the stomach and intestine. In this manner the average fecal sodium content, as sodium chloride, may be increased from the normal of 0.1 to 0.2 gm. to as much as 3 to 4 gm. daily.

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Permutit® Z (WIN 3000) was supplied through the courtesy of The Permutit Company, New York 18, and Winthrop-Stearns, Inc., New York 13.

Clinical material for this study was made available by the Departments of Medicine and Pediatrics of The Jewish Hospital of Brooklyn and the Jewish Sanitarium and Hospital for Chronic Diseases.

1. Dock, W.: Sodium Depletion as a Therapeutic Procedure: The Value of Ion-Exchange Resins in Withdrawing Sodium from the Body, Tr. A. Am. Physicians **59**:282, 1946.

2. Gilwood, M. E.: Personal communication to the author (1947).

3. (*a*) Greenblatt, I. J., and Gilwood, M. E.: Removal of Sodium in Vivo by Permutit Z, in Abstracts of Papers, 113th Meeting of American Chemical Society, Chicago, April 19-23, 1948, Section 2c. (*b*) Greenblatt, I. J.; Cohn, T. D.; Jacobi, M.; Lipschutz, E. W., and Friedman, I. S.: Cation Exchange Polymers in Congestive Heart Failure, Scientific Exhibit, 99th Annual Session of the American Medical Association, San Francisco, June 26-30, 1950. (*c*) Friedman, I. S.; Cohn, T. D., and Greenblatt, I. J.: Use of Cation Exchange Resins in Edema—Treatment of Congestive Heart Failure and the Nephroses, Scientific Exhibit, The Clinical Session of the American Medical Association, Cleveland, Dec. 5-8, 1950.

This exchange resin is completely insoluble in water, acids, or alkalis. It is not absorbed through the gastrointestinal mucosa and, except for exchanging ammonium, passes through the intestinal tract unchanged and may be so recovered. No cation exchanger has been developed which can combine exclusively with one cation and not with the others.

Permutit® Z has an available ultimate exchange capacity of slightly more than 5 mEq. per gram of dry resin, i. e., 29.2 gm. of sodium as sodium chloride per 100 gm. of resin. However, since the exchange resins are not specifically selective of a particular ion, other cations present in the intestinal contents are also removed by the resins. Calcium, potassium, and magnesium ions are taken up even in preference to the sodium ion. Fortunately, their concentration in the intestinal tract is extremely low in comparison with the concentration of the sodium ion. Thus, their interference is comparatively small.[4] The increased fecal excretion of calcium,[5] potassium,[6] and magnesium [5b,c] has been reported. It has also been shown that acidosis [7] and potassium depletion may occur when using hydrogen- or ammonium-exchange resins. To overcome these effects, resin dosage must be carefully adjusted and supplements of potassium and calcium must be given to patients who ingest the exchangers for prolonged periods.

The ammonium ion released by the ammonium-exchange resins in the intestinal tract is presumably absorbed into the blood stream. One hundred grams of permutit® Z is capable of liberating ammonium ions equivalent to 25.7 gm. of ammonium chloride, the chloride coming from the gastrointestinal secretions. The formation of this diuretic agent, ammonium chloride, in conjunction with the simultaneous removal of sodium from the intestinal contents results in the diuresis and aciduria which these patients exhibit.

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4. (*a*) Ch'en, J. S., and Freeman, S.: The Removal of Cations from Solutions and the Rat's Alimentary Canal by H-Form Resins, J. Lab. & Clin. Med. **35**:99 (Jan.) 1950. (*b*) McChesney, E. W.; Dock, W., and Tainter, M. L.: Ion Exchange Resins in Edema, Medicine **30**:183 (May) 1951.

5. (*a*) Footnote 3. (*b*) McChesney, E. W., and McAuliffe, J. P.: Effects of Some Ion Exchange Resins on the Mineral Metabolism of Rats, Am. J. Physiol. **160**:264 (Feb.) 1950. (*c*) Currens, J. H.; Counihan, T., and Rourke, M.: Observations on the Administration of Ammonium Cation Exchange Resin to Patients with Cardiac Edema, J. Clin. Invest. **29**:807 (May) 1950.

6. (*a*) Footnotes 3, 4, and 5. (*b*) Irwin, L.; Berger, E. Y.; Rosenberg, B., and Jackenthal, R.: The Effect of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States, J. Clin. Invest. **28**:1403 (Nov.) 1949. (*c*) Danowski, T. S.; Greenman, L.; Mateer, F.; Peters, J. H.; Weigand, F.; Mermelstein, H., and Clarke, C. E.: Carboxylic Cation Exchange Resin Studies in Animals and Humans, ibid. **29**:807 (June) 1950. (*d*) Dock, W., and Frank, N. R.: Cation Exchangers: Their Use and Hazards as Aids in Managing Edema, Am. Heart J. **40**:638 (Oct.) 1950. (*e*) Hay, S. H., and Wood, J. E., Jr.: Cation Exchange Resins in the Treatment of Congestive Heart Failure, Ann. Int. Med. **33**:1139 (Nov.) 1950. (*f*) Martz, B. L.; Kohlstaedt, K. G., and Helmer, O. M.: Use of Ion Exchange Resins in the Management of Congestive Heart Failure and Cirrhosis of the Liver, J. Lab. & Clin. Med. **36**:962 (June) 1950. (*g*) Kahn, S. S., and Emerson, K., Jr.: Experiences with the Use of Cation Exchange Resins in the Treatment of Edema, J. Clin. Invest. **29**:827 (June) 1950.

7. (*a*) McChesney and others.[4b] (*b*) Currens and others.[5c] (*c*) Martz and others.[6f] (*d*) Friedman, I. S.; Zuckerman, S., and Cohn, T. D.: The Production of Urinary Casts During the Use of Cation Exchange Resins, Am. J. M. Sc. **221**:672 (June) 1951.

PRESENT STUDY

Nineteen patients with congestive heart failure, the nephrotic syndrome, and hepatic disease whose edema had been refractory to the usual forms of therapy were fed varying doses of permutit® Z (35 to 140 gm. daily). In 18 of these patients the edema was favorably influenced. A diuretic response and weight loss were obtained. However, in several of these 18 patients, as described below, resin therapy had to be discontinued in a few days because of untoward effects. The other patients have been able to continue ingesting the resin in adequate doses for prolonged periods. One patient has now been taking the resin for three years. The patient who did not respond was a child with lipid nephrosis. Administration of as much as 50 gm. of the resin daily failed to alleviate the edema.

The use of the exchange resins may be associated with side-reactions, some of which can result in serious consequences. The problems which have been encountered are (1) the production of urinary casts, (2) metabolic acidosis, (3) the low-salt syndrome, (4) hypopotassemia, (5) hypocalcemia, (6) depletion of other electrolytes and substances, and (7) effects upon the gastrointestinal tract (taste, bulk, constipation).

1. *Urinary Casts.*[7d]—All patients, normal human beings, and experimental animals when fed sufficient amounts of the ammonium-exchange resin show numerous granular urinary casts. A trace of protein, but no blood cells, is associated with these casts. The number of casts varies directly with the aciduria which the resin produces. As many as 100 casts per low-power field of a centrifuged urine specimen may be found if enough resin is ingested, usually 75 to 140 gm., to lower the pH of the urine to 5.5 or less. The average therapeutic dose of the resin is 35 to 70 gm. This dose results in a urinary pH of 5.5 to 6, and the number of casts produced is 10 to 30 per low-power field. Discontinuing use of the resin results in the disappearance of these casts within a day or two. The casts apparently form in the distal convoluted or collecting tubules and are readily washed out. All patients who take the resin are urged to drink at least 1,500 ml. of fluids a day. In no instance has any demonstrable deleterious effect developed from the presence of these casts.

Case 1.—Mrs. P. E., aged 46, a patient with chronic rheumatic heart disease, mitral stenosis and insufficiency, auricular fibrillation, and congestive heart failure, had been treated with a salt-poor diet, digitalis, and mercurial injections for more than a year. She was semiambulatory, and, despite the injections being given twice weekly, her edema persisted.

During June, 1948, the administration of mercurial diuretics was discontinued and the use of the ammonium-exchange resin substituted. Since then, her congestive heart failure has been adequately controlled. Her weight decreased from 150 to 136 lb. (68 to 61.7 kg.), and she has not required any mercurial injections. For the past two years her diet has not been restricted and is identical with that of her family, the only limitation being that additional salt is not permitted with her meals. Her present regimen consists of a full diet, 0 to 50 gm. daily of permutit® Z (WIN 3000)—the dose being regulated by herself depending upon her weight—digitalis, and supplements of potassium citrate, 2 gm., calcium lactate, 2 gm., and a multiple-vitamin capsule. She takes the resin in 1-tablespoon (13-gm.) doses at mealtime and, to prevent contact with the resin, the digitalis and supplements at bedtime.

Since the onset of resin therapy this patient has had granular casts in her urine. Early during her course of treatment, when she ingested 100 to 140 gm. of resin daily, her urine contained as many as 100 casts per low-power field. With the dose reduced to 50 gm., numerous casts are

still present. If she omits the resin for a day or two, the urinary sediment promptly reverts to normal. Results of blood chemical studies, including determinations of urea nitrogen, sodium, potassium, chloride, carbon dioxide-combining power, and total proteins, remain normal.

2. *Metabolic Acidosis.*[7]—During the process of ion-exchanging, the ammonium ions released from the exchange resin combine with the anions, primarily chloride, of the gastrointestinal contents to form ammonium chloride. The absorption of this acidic salt and the simultaneous loss of cations in the stool tend to cause a metabolic acidosis. The absorbed ammonium ions are converted in large measure to urea. The renal, respiratory,[6d] and endocrine[8] status of the patient will influence the degree of acidosis and metabolic reactions which occurs. These processes may be reflected in changes in the blood chemical levels. Patients ingesting the resin may have a decrease in the carbon dioxide-combining power, an increase in the chloride, and an elevation of the urea nitrogen of the blood. This occurred in Case 2.

CASE 2.—Mr. M. S., aged 48, a patient with chronic rheumatic heart disease and double aortic and mitral valvular involvement, was admitted to the hospital because of frequent attacks of pulmonary edema. Digitalization, a low-sodium diet, and frequent injections of mercurial diuretics did not suffice to prevent the attacks of left ventricular failure. Administration of the ammonium-exchange resin, 70 gm. daily, and the supplements of potassium, calcium, and multiple vitamins was substituted for the mercurial injections. In six days his weight diminished from 184 to 177 lb. (83.5 to 80.3 kg.). However, he became dyspneic, although his lungs, which previously had been congested, were now clear.

Before resin therapy the blood chemical findings were as follows: urea nitrogen, 10 mg. per 100 ml. and serum sodium, 143 mEq., potassium, 4.3 mEq., chloride, 99 mEq., and carbon dioxide-combining power, 25.8 mM. per liter. Six days later the findings were urea nitrogen, 40 mg. per 100 ml. and serum sodium, 138 mEq., potassium, 4.9 mEq., chloride, 108 mEq., and carbon dioxide-combining power, 11 mM. per liter. The resin administration was discontinued, and he was given 5% sodium bicarbonate solution intravenously. When only 100 ml. of this solution had been administered, an attack of pulmonary edema developed and he died.

In an attempt to overcome this problem of hyperchloremia and acidosis, anion-exchange resins have been added to the cation exchangers.[9] Thus, instead of being absorbed, part of the liberated chloride, phosphate, and sulfate ions in the intestinal tract combine with the anion exchangers and are excreted in the stool. The difficulty here is that, in order to eliminate an appreciable amount of these acidic ions, a large quantity of an anion exchanger must be added. This greatly increases the volume of an already bulky material which these patients have to ingest. Using smaller amounts of the anion exchangers in the resin mixtures is not effective. Acidosis, aciduria, and the formation of large numbers of urinary casts are not prevented.

3. *The Low-Salt Syndrome.*[10]—Strict adherence to a low-sodium diet, frequent injections of mercurial diuretics, or ingestion of excessive amounts of cation-exchange resins may result in the salt-depletion syndrome. Patients with this syndrome may complain of weakness, myalgia, nausea, and vomiting. They may also have oliguria. These symptoms, of varying severity, may or may not be associated

8. Berger, E. Y.; Quinn, G. P., and Homer, M. A.: Effect of Desoxycorticosterone on the Colon: Its Relation to the Action of Cation Exchange Resins in Man, Proc. Soc. Exper. Biol. & Med. **76**:601 (March) 1951.

9. McChesney and McAuliffe.[8b] Martz and others.[6f]

10. Chapman, D. W., and Pannill, C. H.: The Effect of a New Cation Exchange Resin on Edematous States and Electrolyte Balance, J. Lab. & Clin. Med. **36**:808 (Nov.) 1950.

with depression of the serum levels of sodium, potassium, or chloride or elevation of the blood urea. The following case demonstrates the need for considering the patients' weight when prescribing exchange resins.

CASE 3.—Mrs. S. B., aged 40, a patient with chronic rheumatic heart disease, mitral stenosis, tricuspid insufficiency, and hepatomegaly, was admitted to the hospital because of recurrent ascites which necessitated frequent abdominal paracenteses. The rapid reaccumulation of fluid could not be prevented by digitalization, a low-sodium diet, and numerous mercurial injections. Because she was malnourished, weighing only 85 lb. (38.6 kg.) including the ascitic fluid, it was hoped that the resin therapy not only might reduce the need for the many paracenteses but also might permit her to eat a more normal diet.

Her diet was changed to one containing 5 gm. of sodium chloride. Digitalis treatment was continued, and, in addition, she was given 70 gm. of the ammonium-exchange resin daily. The supplements of potassium, calcium, and vitamins were taken at bedtime. In five days she lost 6 lb. (2.7 kg.) but acquired generalized muscular pains, weakness, anorexia, and nausea. Chemical studies of her blood prior to ingesting the resin showed serum sodium to be 148 mEq., potassium, 4.3 mEq., chloride, 95 mEq., and carbon dioxide-combining power, 26mM., per liter. Urea nitrogen was 22 mg. per 100 ml. On the fifth day of resin therapy the findings were as follows: serum sodium, 130 mEq., potassium, 3.6 mEq., chloride, 109 mEq., and carbon dioxide-combining power, 19 mM., per liter, and urea nitrogen, 35 mg. per 100 ml. The resin therapy was discontinued, and she was given a full diet. In two days her symptoms subsided, and she regained all the weight which she had lost. Her blood chemical elements reverted to normal levels. A more favorable response might have been obtained had she been given smaller amounts of the resin.

4. *Hypopotassemia.*[6]—The diuretic and acidotic actions of cation-exchange resins and the increased fecal excretion of potassium may result in potassium depletion. The use of potassium supplements or the addition of a potassium resin to the ammonium or hydrogen resins tends to prevent hypopotassemia. However, when a rapid and marked diuresis is produced, the amounts of potassium in the supplements or in added potassium resin may not be sufficient to maintain positive potassium balance. Case 4 illustrates this type of response.

CASE 4.—Mr. W. W., aged 61, a patient with hypertensive heart disease and severe congestive heart failure, was admitted to the hospital because of anasarca. For a year he had been taking digitalis and a salt-poor diet and had been given mercurial injections two to five times weekly. The injections had been discontinued because of the development of a 4+ urinary reaction for protein. When hospitalized, he weighed 148 lb. (67.1 kg.), his blood pressure was 185/130, and edema extended up to the angles of the scapulas.[1]

A low-sodium diet and digitalis administration were continued, and he was also given the ammonium-exchange resin with potassium, calcium, and vitamin supplements. For six days he took 70 gm. of resin daily. The use of resin was then omitted for one day but was resumed at a dose level of 35 gm. daily for two days. During this nine-day period a profuse diuresis was obtained, and he passed as much as 6,000 ml. of urine per day. His weight fell from 148 to 116 lb. (67.1 to 52.6 kg.). Although he was still slightly edematous, his condition showed considerable improvement. He was more alert and physically stronger, and his appetite returned. His blood pressure was not altered, being 200/140 on the eighth day of resin therapy. On the ninth day he complained of weakness of his lower extremities. The electrocardiogram and serum electrolyte studies now showed the presence of hypopotassemia. There was sagging of the ST segments, with T wave inversion and prolongation of the Q-T intervals. There were no clinical findings of digitalis toxemia in conjunction with the hypopotassemia.[11] The administration of the resin and supplements was discontinued, and he was given a full diet and a potassium mixture which provided 1 gm. of potassium daily. For the following three days he had no complaints. His urinary output was 1,200 to 1,500 ml. daily, and he regained 1 lb. (0.5 kg.) in weight. On the

11. Hay and Wood.[6e] Kraus, H.: The Use of a Cation Exchange Resin in Patients with Cardiac Edema, J. Clin. Invest. **29**:829 (June) 1950.

fourth day, precordial oppression and weakness developed and several hours later he died.[6c] The electrocardiogram and serum electrolyte studies prior to his death revealed hyperpotassemia. The T waves were very tall and peaked. The QRS complexes were widened and the P waves absent.

Chemical analyses of his blood elements before resin therapy showed serum sodium to be 142 mEq., potassium, 5.7 mEq., chloride, 97 mEq., and carbon dioxide-combining power, 20 mM., per liter; urea nitrogen was 37 mg., and creatinine, 2.1 mg. per 100 ml. Nine days later, at the termination of resin therapy, the findings were as follows: serum sodium, 134 mEq., potassium, 4 mEq., chloride, 109 mEq., and carbon dioxide-combining power, 11.4 mM., per liter; urea nitrogen was 45 mg. per 100 ml. Four days later, the day of his death, the blood studies revealed serum sodium to be 142 mEq., potassium, 8.1 mEq., chloride 111 mEq., and carbon dioxide-combining power, 19 mM., per liter. Results of urinalyses before and during the period that he took the resin remained the same. Marked proteinuria and four or five hyaline and granular casts per low-power field were present.

The hypopotassemia which originally developed in this patient is readily explicable on the basis of profuse diuresis, acidosis, and increased fecal potassium excretion. However, the hyperpotassemia which was found four days later cannot be easily explained. The abnormal increase in the serum potassium might have been caused by rapid cellular depletion of potassium, sudden contraction of the extracellular fluid volume, excessive potassium intake in the presence of renal damage, or renal failure to excrete normal amounts of potassium. Which of these processes occurred in this case is unknown. His potassium intake was not excessive, and his urinary volume was 1,200 to 1,500 ml. daily. Nevertheless, since the blood urea nitrogen was elevated and severe proteinuria was present, it is probable that renal damage was a factor in causing the serum potassium elevation. The reinstitution of cation-exchange-resin therapy during the period of hyperpotassemia might have been of value in lowering the serum potassium.[12]

It has been reported that cation-exchange resins are of value in the control of hypertension.[13] In the above case there was no demonstrable effect upon the elevated blood pressure. The hypertension of four other patients who ingested cation-exchange resins was not affected by this form of therapy. However, the elevated blood pressures of these five patients were complicated by congestive heart failure.

5. *Hypocalcemia.*[5]—Patients with renal involvement or those who ingest the cation exchangers for prolonged periods may show hypocalcemia. All these resins, the carboxylic more so than the sulfonic, have a greater affinity for calcium than for potassium or sodium.[5b] Fortunately, the monovalent cations are present in the intestinal tract in greater quantity than the divalent ones. Reports concering calcium balance studies with exchange resins are conflicting.[14] However, hypocalcemia and carpopedal spasm have been observed during the use of these exchangers.[6g] To avoid this, these patients are given calcium lactate supplements at bedtime. Case 5 illustrates the rapid development of hypocalcemia.

CASE 5.—Miss J. G., aged 21, a patient in the nephrotic stage of glomerulonephritis of two years' duration, was admitted to the hospital because of progressive edema. Her blood pressure

12. Elkinton, J. R.; Clark, J. K.; Squires, R. D.; Bluemle, L. W., Jr., and Crosley, A. P., Jr.: The Treatment of Potassium Retention in Anuria with a Cation Exchange Resin, Am. J. M. Sc. **220**:547 (Nov.) 1950.

13. Groff, D. N.: A Cation Exchanger in Hypertension, New York J. Med. **51**:758 (March 15) 1951.

14. Greenblatt and Gilwood.[3a] Currens and others.[5c] Footnote *6b* and *d*.

was 110/80. The renal-function studies showed a diminution in urea clearance, urine concentration, and phenolsulfonphthalein excretion. There was 16 to 20 gm. of protein in the daily urine specimen, and the sediment contained 8 to 10 hyaline and granular casts per low-power field of a centrifuged specimen.

For eight days, in addition to a low-sodium diet, she was given 50 gm. of the ammonium-exchange resin daily. The potassium, calcium, and vitamin supplements were taken at bedtime. During this period she lost 12 lb. (5.4 kg.), her weight decreasing from 148 to 136 lb. (67.1 to 61.7 kg.). A week after the resin treatment was discontinued, her weight returned to 148 lb. At no time were there any clinical signs of electrolyte depletion. While she was taking the resin, the number of casts in the urinary sediment increased to 25 to 30 per low-power field.

Blood chemical analyses before resin therapy showed serum sodium to be 147 mEq., potassium, 5.9 mEq., chloride, 110 mEq., and carbon dioxide-combining power, 22.7 mM., per liter; urea nitrogen was 10 mg., uric acid, 4.6 mg., total cholesterol, 580 mg., and total protein, 4.2 gm., per 100 ml., with an albumin-globulin ratio of 0.4. Calcium measured 5.2 mEq. and phosphorus 2.2 mEq. per liter. During the period of exchange-resin ingestion, the following changes occurred: Serum sodium became 134 mEq., potassium, 5.2 mEq., chloride, 128 mEq. and carbon dioxide-combining power, 16.3 mM., per liter; urea nitrogen measured 21 mg. and uric acid 6.2 mg., per 100 ml., and calcium was 4 mEq. and phosphorus 2.4 mEq. per liter. There were no changes in the other blood constituents.

In the presence of acidosis, although the total serum calcium may be low, the ionizable fraction may remain normal. Patients having hypocalcemia with this pattern may, therefore, show no clinical manifestations of neuromuscular irritability. The development of osteomalacia must also be considered in those instances in which the cation resins are taken for long periods. Thus far, there has been no evidence of this. There have been no demonstrable changes in phosphorus metabolism.[4a] The use of anion-exchange resins may, however, affect phosphorus balance.

6. *Depletion of Other Electrolytes and Substances.*[15]—The cation-exchange resins, in addition, will take up other cationic substances from the intestinal contents. These include magnesium and iron, some of the vitamins of the B complex (thiamine and riboflavin), and some of the amino acids and amine compounds, such as putrescine and cadaverine.[2]

Streptomycin, when given by mouth, and alkaline medicaments, such as quinine, scopolamine, and atropine, which are alkaloids, may also in part be removed by the cation exchangers. The other antibiotics for oral administration which are chemically neutral or which have exceedingly large molecular structures will probably not be affected. Studies involving these products have not as yet been carried out. If anion exchangers are also added, then acidic substances, including chloride, phosphate, sulfate, penicillin, nicotinic acid, and ascorbic acid, may be picked up and removed in the stool. This also has not been investigated thoroughly.[2] Magnesium metabolism can be disturbed directly by the fecal loss of magnesium or indirectly by its close relationship to calcium and potassium metabolism.[16] The symptoms of weakness and neuromuscular irritability which have been attributed to calcium and potassium loss may, to some degree, be due to magnesium depletion. To avoid this, patients taking the resin are given 4 gm. of magnesium sulfate once weekly at bedtime.

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15. Gilwood.[2] Footnote 3. McChesney and others.[4b] Footnote 6*b* and *d*.

16. Engel, F. L.; Martin, S. P., and Taylor, H.: On Relation of Potassium to Neurological Manifestations of Hypocalcemic Tetany, Bull. Johns Hopkins Hosp. **84**:285 (April) 1949.

No signs of iron or vitamin deficiency have been observed in any of the patients who have been taking the exchange resins for one to three years. Because of the more normal diet which they are permitted, their nutritional status has actually been improved. Reports of balance studies have shown that cation-exchange resins do not disturb nitrogen balance.[6b,c]

Exchange-resin interference with drug absorption has not as yet been investigated. This problem arose during the management of a patient with rheumatic heart disease and congestive heart failure. She was responding well to exchange-resin therapy when atypical pneumonitis developed. Administration of the resin was discontinued, and she was given chloramphenicol. When the pneumonitis subsided, resin therapy was reinstituted.

7. Gastrointestinal Effects.—The taste, consistency, bulk and constipating effect of the various exchangers have made it difficult for some patients to ingest the resins.[17] Owing to the rapid release of hydrogen, the hydrogen exchangers may cause buccal puckering and a sensation of epigastric burning. The particles of the ammonium sulfonic resin, when used in a fine granular form, lodge between the teeth. In powder form this resin has a constipating action. The carboxylic resins, both hydrogen and ammonium forms, because of their consistency and greater bulk, are even more constipating and produce a putty-like stool. One of our patients while taking a hydrogen carboxylic resin had a fecal impaction. The even greater volume of a combination of three resins (polyamine resin and potassium and hydrogen carboxylic resins), when taken in adequate dosage, causes a feeling of abdominal fulness and decrease in appetite.

CONCLUSIONS

The use of cation-exchange resins may result in disturbances of the acid-base balance of the body and the loss of essential cations and other necessary substances.

Hyperchloremia, acidosis, and elevation of the blood urea nitrogen were most commonly observed.

Hypopotassemia and hypocalcemia may also occur. As yet, studies pertaining to the loss of magnesium, the vitamins of the B complex, and medicaments have not been done.

Granular casts form in the urine of all patients who are given effective doses of the resins. No ill effects due to these casts have been noted.

All patients, particularly those with renal involvement,[18] require careful supervision and blood electrolyte determinations during exchange-resin therapy.

To avoid the development of depletion states, supplements of potassium, calcium, magnesium, and the vitamins of the B complex should be given to these patients.

17. Kleiber, E. E., and Pickar, G.: Treatment of Chronic Congestive Cardiac Failure with Ion Exchange Resins, Ann. Int. Med. **34**:407 (Feb.) 1951.

18. Friedman and others.[7d] Lippman, R. W.: Sodium Adsorbent Resins—Warning, Correspondence, J. A. M. A. **146**:395 (May 26) 1951.

Case Reports

GEOTRICHUM SEPTICEMIA

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A FEW INSTANCES of Geotrichum infection of the bronchopulmonary system have been described,[1] but, as far as can be ascertained, no case of septicemia or mycethemia due to Geotrichum has ever been recorded in the medical literature. The clinical response to neomycin, despite the advanced age of the patient, a diabetic under poor control, is another point of interest in the case here reported.

REPORT OF CASE

I. W., a white man 79 years of age, complained of extreme weakness, anorexia, loss of weight, chills, and fever in August, 1950.

Clinical History.—The patient had been in good health until 1947, when diabetes mellitus was discovered. He did well with a controlled diet and a daily dose of 25 units of protamine zinc insulin injection until April, 1949, when he accidentally burned his left lower leg. The diabetes then became very much aggravated; he spilled large amounts of sugar in his urine, and, in spite of increased insulin dosage and an adequate diet, he continued to lose weight (about 15 lb. [6.8 kg.] in two weeks). The burn healed well. During that time he also complained of difficulty on urination and of frequency, with slight vague discomfort in the lower part of the abdomen. Hypertrophy of the prostate, with possible malignant growth, was diagnosed. Renal function tests gave normal results. The prostate was removed in a one-stage suprapubic operation on July 19, 1949. A few days later he had postoperative phlebitis of the legs, for which bilateral ligations of the femoral veins were performed. Convalescence was uneventful, until his diabetes was again exacerbated by cystitis, due to Candida albicans, in August, 1950. Bladder instillations of methylrosaniline chloride (gentian violet), and 250 mg. of chloramphenicol (chloromycetin®) given orally four times a day, checked the clinical evidence of urinary-tract infection, though yeasts were frequently found on subsequent examinations of the urine. He did well for about a year with a controlled diet and use of protamine zinc insulin injection.

Present Illness.—In August, 1950, while away from home, the patient deviated from his controlled diet for three weeks, and pronounced glycosuria and hyperglycemia developed. He became very asthenic and acquired pharyngitis. The temperature was 101 F., the pulse rate 78, and the respiratory rate 20. The urinary reaction for sugar was 4+, and an abundance of unidentified yeasts was found in repeated urine specimens. Intramuscular injections of 400,000 units of penicillin and 250 mg. of chloramphenicol every four hours for two days brought the temperature down to normal. Three days later he had a chill; his temperature rose to 102 F., and he complained of malaise and weakness. His appetite was poor, and he appeared dehydrated. Intravenous infusions of isotonic sodium chloride solution, to which was added 400 mg. of aureomycin, were given twice daily till the temperature became normal on the third day. A blood culture, taken before aureomycin therapy was instituted, was reported as yielding no

† Dr. Bendove died Sept. 21, 1951.

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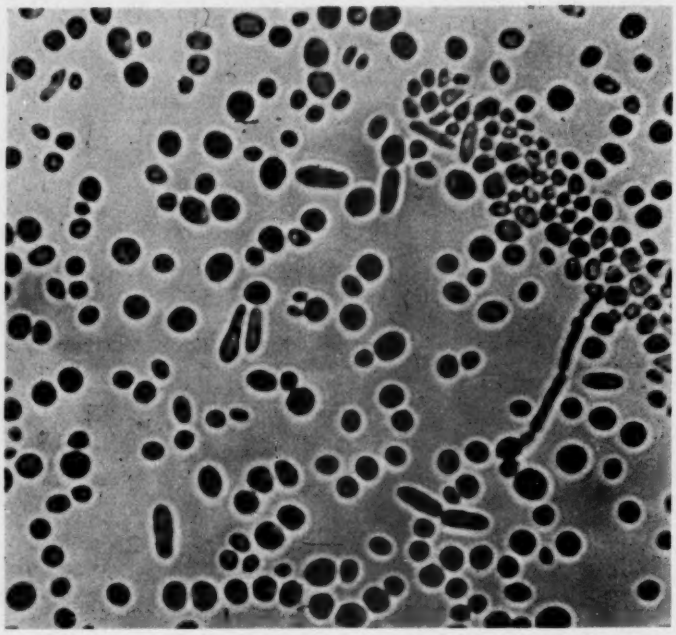
1. Kunstadter, R. H.; Pendergrass, R. C., and Schubert, J. H.: Bronchopulmonary Geotrichosis, Am. J. M. Sc. **211**:583, 1946. Smith, D. T.: Oidiomycosis of the Lung, J. Thoracic Surg. **3**:241, 1934.

pathogens. Glycosuria was marked, and the fasting blood-sugar level was 390 mg. per hundred cubic centimeters. A few days later he experienced another chill, followed by an elevation in temperature to 103 F. and accompanied with sweating and paroxysmal tachycardia of 120 to 130 beats per minute, which lasted half an hour. The blood pressure was 120/80. He began to experience transitory pain and tenderness in the left costovertebral angle. The urine contained many yeasts. The temperature ranged from 100 to 102.5 F. None of the available antibiotics, given singly or in combination, hand any appreciable effect. Blood chemical values were normal, except for hyperglycemia, the blood sugar measuring 380 mg. per hundred cubic centimeters. The hemoglobin concentration was 92% (Sahli); the red-blood-cell count was 4,450,000, and the white-blood-cell count 9,000 per cubic millimeter, with 68% polymorphonuclear cells. The sedimentation rate was 42 mm. in one hour (Wintrobe, corrected). A chest roentgenogram was normal, as was an electrocardiogram. Traces of acetone appeared in the urine. The carbon-dioxide-combining power was 46 vol. %.



Geotrichum sp. found in blood culture of patient. Note thick-walled spherical cells and, particularly the oblong and rectangular forms which are characteristic of Geotrichum.

Course in Hospital.—He was admitted to the University Hospital, New York City, on Sept. 14, 1950. The fever continued. His fasting blood-sugar level was 330 mg.; the carbon-dioxide-combining power was 43 vol. %; the hemoglobin concentration was 10 gm., the red-blood-cell count 3,400,000, and the white-blood-cell count 12,150, with 91% polymorphonuclear forms. The sedimentation rate was 90 mm. in one hour. Repeated chest roentgenograms and electrocardiograms were again normal. A rare premature ventricular contraction was noted. Glycosuria (a total of 70 gm. of sugar was excreted in 24 hr.) responded to four or five injections of regular insulin daily, until on the eighth day the urinary-sugar level fell to 15 gm. Treatment was then continued with one injection of 40 to 60 units of globin zinc insulin injection, with little or no glycosuria. A mild degree of congestive heart failure responded quickly to diuretic and digitalis therapy. He continued losing weight and appeared cachectic.

Blood cultures made on Sept. 24 and 27 both showed a fungus identified as Geotrichum sp. (Fig.). A sputum culture yielded Geotrichum; urine cultures were negative for Geotrichum but contained Candida albicans. The patient received a transfusion of 500 cc. of blood on Oct. 3, and neomycin therapy was initiated.

Administration of neomycin sulfate, 1,000 units per kilogram of body weight daily, in four divided doses intramuscularly, was begun on Oct. 5 and continued through Oct. 7. From Oct. 8 to 17, the dosage was 500 units per kilogram of body weight. We are indebted to Dr. Wolgamot[2] both for his outline of the therapy and for the neomycin with which he supplied us.

The temperature elevation subsided gradually. A transfusion of 500 cc. of blood was again given on Oct. 13. Blood cultures on Oct. 9 and 13 were still positive for Geotrichum. The patient showed signs of impaired hearing on the 11th day of neomycin therapy, and administration of the drug was discontinued soon thereafter. His blood urea nitrogen, which had been 22 mg. per hundred cubic centimeters on Sept. 20, rose to 34 mg. on Oct. 7 (the fourth day of neomycin therapy); it has since reverted to normal with cessation of treatment with the drug.

Present Status.—The patient was discharged from the hospital on Oct. 17, 1950, and rest in bed was continued at home for two weeks. Blood cultures taken Oct. 20 and 27 were negative for pathogens. The hemoglobin concentration was 9.5 gm.; the erythrocytes numbered 3,100,000 and the leucocytes 8,400. He was given a transfusion of 500 cc. of blood on Oct. 23. His diabetes has been well controlled by a diet containing 200 gm. of carbohydrate, 80 gm. of protein, and 100 gm. of fat, with a total of 2,020 calories daily, and the use of 35 units of globin zinc insulin injection daily. He has regained 30 lb. (13.6 kg.), feels well, and is up and about. The sputum still contains Geotrichum occasionally, but there are no clinical manifestations of infection. His deafness persists.

COMMENT

The genus Geotrichum contains several species which have been isolated from the stool and from the sputum of apparently normal persons.[3] The clinical types of Geotrichum infection, as reported in the literature, are either lesions of the bronchi resembling chronic bacterial bronchitis or lesions of the lungs simulating pulmonary tuberculosis in their clinical course, physical signs, and roentgenologic appearance. None of these manifestations was observed in the case here reported. The dominant clinical picture of the present case was that of an acute septicemia or bacteremia, the causative agent of which was found to be a fungus. A fatal case of mycotic endocarditis, described by Joachim and Polayes,[4] was caused by a species of Candida which was isolated from the blood culture and from the vegetations of the heart valves. It is possible that the endocardium was involved in the present case, but this could not be confirmed clinically, so that the diagnosis of mycethemia (i. e., a blood-stream infection with a fungus) due to Geotrichum is preferable.

The problem of the primary focus of infection is baffling. Suspicion was focused upon the urinary tract, which was infected with Candida albicans after the patient's prostatectomy. However, no growth of the Geotrichum was recovered from the urine. The detection of the Geotrichum in the sputum makes it likely that the portal of entry was the upper respiratory tract. The patient may have harbored the Geotrichum organisms in his mouth for a long time prior to the mycethemia without symptoms. The Geotrichum can still be isolated from the sputum, though

2. Wolgamot, J. R.: Personal communications to the authors.

3. Schnoor, T. G.: Stools of Normal People, Am. J. Trop. Med. **19**:163, 1939. Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944.

4. Joachim, H., and Polayes, S. H.: Subacute Endocarditis and Systemic Mycosis, J. A. M. A. **115**:205 (July 20) 1940.

he is asymptomatic and is gaining weight persistently. The invasion of the blood stream probably occurred at the time of his pharyngitis, when he was in a debilitated state associated with uncontrolled diabetes; the marked hyperglycemia may have favored the growth of the fungi, which are known to thrive on dextrose mediums.

The mode of action of neomycin on the Geotrichum, whether fungicidal or fungistatic, or both, can only be conjectured. Duncan, Clancy, Wolgamot, and Beidleman,[5] in their laboratory and clinical investigations on the effectiveness of antibiotics on various pathogenic organisms, found the Geotrichum sensitive to neomycin and resistant to aureomycin and to streptomycin. The in vitro activity of neomycin on the Geotrichum in the case here reported was slight, yet clinically it seemed to be the only therapeutic agent which checked the downhill febrile course of the patient; it rendered his blood sterile after 12 days of therapy. Waksman, Lechevalier, and Harris[6] observed that glucose reduces the activity of neomycin. This reduced activity in the presence of the patient's diabetes may perhaps explain why the blood still contained the Geotrichum organisms after eight days of neomycin administration. The persistence of the organism in the sputum, despite prolonged neomycin therapy, suggests that the neomycin had only a suppressive or fungistatic effect on the Geotrichum.

The toxic reactions produced by the neomycin were persisting deafness and a rise in blood urea nitrogen which reverted to normal after cessation of therapy.

SUMMARY

A case of Geotrichum mycethemia in a diabetic man 79 years of age is reported. Neomycin seemed to be the only therapeutic agent which checked the patient's febrile downhill course; its use rendered his blood sterile after 12 days of treatment. The Geotrichum is still found occasionally in his sputum, but there are no clinical manifestations of infection. His deafness, which resulted from the neomycin therapy, still persists.

5. Duncan, G. G.; Clancy, C. F.; Wolgamot, J. R., and Beidleman, B.: Neomycin: Results of Clinical Use in 10 Cases, J. A. M. A. **145**:75 (Jan. 13) 1951.

6. Waksman, S. A.; Lechevalier, H. A., and Harris, D. A.: Neomycin: Production and Antibiotic Properties, J. Clin. Invest. **28**:934, 1949.

NEW SYMPTOMATIC TREATMENT FOR ACUTE INTERMITTENT PORPHYRIA

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HERETOFORE there has been no satisfactory treatment for acute intermittent porphyria.[1] Mortality and morbidity have been high.[1b] The gastrointestinal disability alone has prevented patients from being self-supporting since the sequelae of one exacerbation persist as the next exacerbation begins. Frequently patients with initial symptoms limited to the gastrointestinal tract later exhibit neurological symptoms.[1b] When neurological symptoms appear, the mortality approaches 90% in a single attack.[2]

Prolonged observation of frequently occurring exacerbations of acute intermittent porphyria in one patient afforded opportunity to test the effectiveness of several new treatments. Four successful methods were discovered which promptly aborted symptoms. The patient was able to return to employment from which his illness had kept him for the preceding two years.

REPORT OF CASE

D. S., a 28-year-old white man, entered the hospital in January, 1948, complaining of severe abdominal pain, nausea, and vomiting. He had considered himself well, except for a deformity of the skull present since birth, until six months previously, when he episodically began experiencing abdominal pain, nausea, and vomiting lasting up to a few days each time. He passed dark urine during the attacks. Appendectomy had produced no improvement. His father had experienced similar distress for many years. Opportunity to examine the father was not permitted.

The patient was experiencing acute distress. He was 67½ in. (171.5 cm.) tall and weighed 120 lb. (54.4 kg.). His usual weight was 135 lb. (61.2 kg.). Oxycephaly was present. His teeth were pitted and discolored. The abdomen was tender, and the abdominal muscles were resistant to palpation.

The urine color varied between dark "port wine" and mahogany. It darkened on standing. When freshly passed, urine made alkaline by oral sodium bicarbonate administration was lighter than was urine with an acid reaction. Porphobilinogen was demonstrated in dilutions of urine with up to 25 parts of water by the test of Watson and Schwartz.[3] In a series of sulfobromophthalein (bromsulphalein®) sodium tests, there was between 15 and 30% retention of the drug, 45 minutes after intravenous administration of 5 mg. per kilogram of body weight.

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Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Nesbitt, S.: Acute Porphyria, J. A. M. A. **124**:286-294 (Jan. 29) 1944. (*b*) Waldenström, J.: Studien über Porphyrie, Acta med. scandinav., Supp. 82, pp. 1-254, 1937.

2. Mason, V. R.; Courville, C., and Ziskind, E.: The Porphyrins in Human Disease, Medicine **12**:355-439, 1933.

3. Watson, C. J., and Schwartz, S.: A Simple Test for Urinary Porphobilinogen, Proc. Soc. Exper. Biol. & Med. **47**:393-394, 1941.

When the patient was examined peritoneoscopically,[4] there was no free fluid in the abdomen. The liver was somewhat increased in size with slight thickening of Glisson's capsule and was dark brown. The border was soft and flexible. There were some engorgement of the gastric veins and thickening of the serosa of the stomach. During the examination, which was begun when the patient was free of pain, he complained of severe abdominal cramping. Then peristalsis stopped, and injection of the serosa of the loops of bowel in the upper abdomen appeared. The observer felt these changes might be of significance, but he had seen similar changes in patients with cramps during peritoneoscopy who did not have porphyria. Histologically the liver showed slight increase in periportal connective tissue, and in places thin strands of connective tissue extended into the liver lobules along the sinuses. There was also a small amount of finely granular brown pigment throughout the liver parenchyma, especially about the central sinusoids. Only a small amount of this pigment stained with iron stains, and most of such positive-staining pigment was in the Kupffer cells.

Initially, the patient was treated supportively and with analgesic drugs, including codeine, morphine, meperidine hydrochloride, and methadone hydrochloride. Use of these drugs gave incomplete relief of short duration. No significant alteration in his condition resulted from complete elimination of barbiturates, a diet free of green vegetables and glandular meats, or intake of large quantities of all the vitamins. Intramuscular administration of crude liver extract was without effect. Intravenous injections of calcium gluconate (2-gm. dose) and magnesium sulfate did not alter the pain.

The attack which led to hospitalization lasted one month. Abdominal pain was somewhat variable from day to day, generally increasing in the first week, remaining at great severity the second and third weeks, and gradually disappearing by the end of the month. In the second week he became confused, disoriented, and hallucinated and at this time only showed a high but variable blood pressure. The mental symptoms lasted about a week. Because of persistent nausea and vomiting, he lost weight and strength despite parenteral feedings.

In the first 14 months of observation, the patient experienced recurrent periods of abdominal pain, nausea, and vomiting lasting two weeks to a month and a half separated by asymptomatic periods lasting two weeks to a month. He spent 148 days (35% of his time) in the hospital. With some attacks of abdominal pain and occasionally independently, he experienced severe deep aching pain in the muscles of the buttocks and legs. In the first few hours after the onset of muscular pains, the knee and ankle reflexes were hyperactive and sustained ankle clonus could be demonstrated. On the subsequent day these signs were invariably absent, although the muscular pains would occasionally persist as long as a week. Never was areflexia noted, and never was there any similar distress above the buttocks.

In the 14th month of observation, 0.33 mg. of epinephrine was injected slowly intravenously. Dr. F. W. Hoffbauer [5] had observed "very transient relief from abdominal cramps" in another patient after epinephrine administration. D. S., however, experienced unusually severe aggravation of his abdominal pain which could not be relieved by administration of ½ grain (30 mg.) of morphine. Two hours later, 150 mg. of tetraethylammonium (etamon®) chloride injected intravenously produced immediate, complete relief of abdominal pain. Within a few hours the pain recurred and was relieved by intramuscular injection of the same drug. Occasional injections were given in the next few days and likewise produced control of pain. Within a week the pain ceased to recur; he began to eat well; he gained in weight (his body weight had fallen to 87 lb. [39.5 kg.]) and in strength. Within a month, he returned to his first employment in almost two years.

In the next eight months tetraethylammonium chloride, when used, promptly aborted each attack. Doses varying between 100 and 450 mg. intravenously were equally effective. Tubocurarine chloride was given intravenously for treatment of some attacks in doses of ½ unit per pound (0.15 mg. per kilogram) of body weight. It likewise produced immediate, complete relief. The patient carried on full employment.

After the eight-month period of easy control (November, 1949), a particularly severe episode of abdominal pain, deep aching in buttocks and legs, nausea, vomiting, and constipation occurred. The patient did not seek medical help until the third day, a longer period than he

4. Peritoneoscopy was performed by Thomas Horan, M.D., Detroit.

5. Hoffbauer, F. W.: Personal communication, University of Minnesota Medical School.

had previously waited. At this time use of tubocurarine chloride gave only transient relief of pain and treatment with tetraethylammonium chloride gave no improvement. Administration of 75 mg. of 2-benzyl-4,5-imidazoline (priscoline®) hydrochloride intravenously was followed by an hour's relief. Use of piperoxan (benodaine®) hydrochloride gave no relief. Treatment with glyceryl trinitrate (1/100 grain [0.6 mg.] sublingually) and atropine (1/100 grain [0.6 mg.] intravenously) was likewise without favorable effect. Morphine administration produced only slight relief. The patient remained in severe pain, practically without sleep or food intake for several days. Thereafter some waxing and waning of the pain occurred, but it did not cease. On Oct. 6, a posterior splanchnic block was induced with injection of procaine hydrochloride. Immediate relief of abdominal pain lasting 24 hours took place, after which the pain recurred. The abdominal pain persisted with variable intensity for the next two months. Toward the end of the period, improvement would follow tetraethylammonium chloride injections.

No further attacks of the severity of the attack beginning in November, 1949, have occurred. The patient has reported for treatment promptly, however, when he has begun to experience pain. All subsequent attacks have been promptly and completely relieved by injections of either tetraethylammonium chloride or tubocurarine chloride.

COMMENT

Sympathetic ganglions of patients with acute intermittent porphyria frequently reveal lesions at necropsy.[6] Mason and associates [2] found spasmodic contraction of the bowel throughout its entire length at operation on a patient with an acute attack of acute intermittent porphyria and attributed this contraction to the lesions of the sympathetic ganglions. D. S. also showed complete cessation of peristalsis during an attack of pain. Gordin [7] drew attention to the sympatheticotonia manifested by tachycardia, restlessness, and dilated pupils in patients with porphyria and suggested therapy with neostigmine (prostigmin®) in an effort to counterbalance the sympatheticotonia by increasing vagal stimulation. His patient improved after neostigmine treatment; D. S. has not received it.

Tetraethylammonium chloride is a ganglionic blocking agent [8] producing interruption of transmission at sympathetic and parasympathetic ganglions. Priscoline® hydrochloride blocks sympathetic pathways at their termination in smooth muscle and has an adrenolytic action.[9] The procaine-induced splanchnic block interrupts preganglionic and postganglionic sympathetic fibers but may also influence transmission in ganglions in the field of the injection. The site of action of tubocurarine chloride is less well localized. Gross and Cullen [10] showed that administration of therapeutic amounts of curare caused relaxation of the smooth muscle of the small intestine and that this effect was due, in part, to a direct action on the effector cells. They felt that their experiments also corroborated the growing concept that

6. Mason and others.[2] Baker, A. B., and Watson, C. J.: The Central Nervous System in Porphyria, J. Neuropath. & Exper. Neurol. **4**:68-76, 1945. Little, N., and Palmer, H.: Acute Porphyria: A Case Report with Notes on 4 Others, New Zealand M. J. **47**:461-471, 1948.

7. Gordin, R.: Prostigmin vid akut porfyri, Nord. med. **37**:480-481, 1948.

8. Acheson, G. H., and Moe, G. K.: The Action of Tetraethylammonium Ion on the Mammalian Circulation, J. Pharmacol. & Exper. Therap. **87**:220-236, 1946.

9. Grimson, K. S.; Reardon, M. J.; Marzoni, F. A., and Hendrix, J. P.: The Effects of Priscol (2-Benzyl-4,5-Imidazoline HCl) on Peripheral Vascular Diseases, Hypertension, and Circulation in Patients, Ann. Surg. **127**:968-990, 1948. Grimson, K. S.; Hendrix, J. P., and Reardon, M. J.: Newer Adrenolytic, Sympatholytic, and Ganglionic Blocking Drugs, J. A. M. A. **139**:154-155 (Jan. 15) 1949.

10. Gross, E. G., and Cullen, S. C.: The Action of Curare on the Smooth Muscle of the Small Intestine and the Blood Pressure, Anesthesiology **6**:231-238, 1945.

curare is capable of acting anywhere in the nervous system that acetylcholine is the chemical mediator. Piperoxan hydrochloride is adrenolytic, but its action is of extremely short duration. Its fleeting action can explain its apparent lack of effect.

The reason for failure of tetraethylammonium chloride treatment to relieve unusually severe pain experienced by the patient in November is obscure. The largest dose employed (7 mg. per kilogram of body weight) may have blocked ganglionic transmission only incompletely or a higher concentration of porphyrins may have acted peripheral to the ganglions. Porphyrins, particularly the tetrabasic coproporphyrins, in sufficient concentration, cause spastic contraction of isolated intestinal strips of animals.[11] The subsequent relief induced by splanchnic block does not clarify the problem, since the block could have completely inhibited sympathetic transmission or porphyrin concentrations could have fallen in the interval to a level adequate to produce increased sympathetic impulses but inadequate to stimulate the bowel wall directly. Subsequent trial with tetraethylammonium chloride established its continued effectiveness, eliminating the consideration of acquired resistance to its action.

Relief induced by blocking the sympathetic nervous system at diverse sites in this patient supports Mason's [2] hypothesis that pain is related to abnormalities of this system. The infrequency of patients with acute intermittent porphyria prevents more thorough trial immediately of the new treatment. It is hoped that others will test it.

SUMMARY

A patient with frequent exacerbations of acute intermittent porphyria, manifested by abdominal pain, nausea, vomiting, and cramps in legs and buttocks, was observed for two and one-half years.

Relief of symptoms was produced by injections of tetraethylammonium (etamon®) chloride, 2-benzyl-4,5-imidazoline (priscoline®) hydrochloride, or tubocurarine chloride or by induction of splanchnic sympathetic block.

State University of Iowa College of Medicine.

11. Reitlinger, K., and Klee, P.: Zur biologischen Wirkung der Porphyrine, Arch. exper. Path. u. Pharmakol. **127**:277-286, 1928.

Progress in Internal Medicine

INFECTIOUS DISEASES

Seventeenth Annual Review of Significant Publications

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THE ADVANCES made in the field of infectious diseases during the last two decades are reflected in these annual reviews by the prominence given them. Indeed, the history of these years can be divided into distinct periods based on a succession of epochal therapeutic discoveries. After the first review published in 1935, pneumococcic pneumonias and their treatment with specific antipneumococcic serum held the chief interest up to 1939, when serum was displaced by sulfapyridine. Sulfonamide chemotherapy for many infections dominated interest until 1944. Penicillin was referred to briefly in 1942, the year that serotherapy last was mentioned. Two years later penicillin treatment rendered sulfonamide chemotherapy almost obsolete. Penicillin and the discovery of a surprising variety of other antibiotic agents placed them as leading subjects since 1944. At present, effects of adrenocorticotropic hormones on infectious diseases are under intensive study. So far, however, aside from immediate beneficial effects in rheumatic disease and possibly in typhoid, hormonal therapy is not of much value in infectious diseases, and, in fact, it is harmful in many respects.

ADRENAL STEROIDS AND INFECTIOUS DISEASES

Most of the work on adrenal steroids and infectious diseases published up to March, 1951, was reviewed elsewhere.[1] A few of the many papers published since then are considered here. Most evidence suggests that corticotropin (ACTH) and cortisone administration has no significant effect on the formation of antibodies. Reports of the action of both agents on human disease and in animals experimentally infected are conflicting and vary with the infection studied and the mode and amount of therapy. The temporary beneficial effects of the agents on acute rheumatic fever, rheumatoid arthritis, and typhoid are of interest, but harmful effects during certain infections and untoward side-effects are serious matters. In general, whatever effect does occur involves chiefly the host, not the microbe. Inflammatory reaction, fever, vascular changes, and leucocytic infiltration caused by a variety of irritants, including allergy, are inhibited by hormonal activity.

In tests on animals, cortisone and corticotropin depressed the formation of connective and granulation tissue,[2] inhibited the formation of antibody,[3] and interfered with the lymphocytes. Cortisone delayed the early inflammatory changes in the

1. Kass, E. H., and Finland, M.: The Role of Adrenal Steroids in Infection and Immunity, New England J. Med. **244**:464-470 (March 29) 1951.

2. Ragan, C., and others: The Effect of ACTH and Cortisone on Connective Tissue, Bull. New York Acad. Med. **26**:251-254 (April) 1950.

3. Fischel, E. E.: The Relationship of Adrenal Cortical Activity to Immune Responses, Bull. New York Acad. Med. **26**:255-260 (April) 1950.

skin [4] and reduced the phagocytic activity of neutrophilic leucocytes.[5] Corticotropin therapy failed to protect mice against the toxic effects of either influenza virus or the Rickettsia of typhus.[6] In tests using intradermal pneumococcic infection in rabbits, animals treated with cortisone suffered fulminating inflammation, and most of them died in 4 to 10 days. Untreated animals had small lesions, and most of them recovered.[7] In other experiments, cortisone caused pneumonia induced in rats with pneumococci or staphylococci to become much severer than in untreated ones.[8] Cortisone-treated rabbits had septicemia and died after inoculation with numbers of streptococci too small to affect untreated animals. However, specific immunization before treatment prevented death, suggesting that cortisone does not interfere with the mechanism of immunity.[9] Mice infected with pneumococci and treated with corticotropin lived a few hours longer than control animals; those given cortisone died sooner. Partly immunized mice were not benefited by either corticotropin or cortisone. Corticotropin had no influence on mice infected with influenza virus.[10] The divergent action of these hormones in causing benefit in some instances and harm in others makes it inadvisable to use them as therapeutic agents until much more is learned about their action. Cortisone caused an increase in the severity of poliomyelitis in mice and enhanced their susceptibility to infection with other neurotropic viruses.[11] The action of cortisone in interfering with resistance to infection was used to establish infection with Coxsackie virus in adult mice, which ordinarily are not as susceptible as suckling mice.[12] Perhaps this procedure may be fruitful in isolating other elusive viruses against which animals heretofore have been insusceptible, as, for example, the causative agents of viral pneumonia, viral dysentery, and viral hepatitis.

Of two groups of 87 patients each, with hemolytic streptococcic infections of the respiratory tract, those who received cortisone had fever longer than the untreated patients. Acute rheumatic fever developed in two who received cortisone.

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4. Michael, M., and Whorton, C. M.: Delay of the Early Inflammatory Response by Cortisone, Proc. Soc. Exper. Biol. & Med. **76**:754-757 (April) 1951.

5. Crepea, S. B.; Magnin, G. E., and Seastone, C. V.: Effect of ACTH and Cortisone on Phagocytosis, Proc. Soc. Exper. Biol. & Med. **77**:704-706 (Aug.) 1951.

6. Kass, E. H.; Neva, F. A., and Finland, M.: Failure of ACTH to Protect Against Lethal Toxins of Influenza Virus and Rickettsiae, Proc. Soc. Exper. Biol. & Med. **76**:560-563 (March) 1951.

7. Robinson, H. J.: Effects of Cortisone on Intradermal Pneumococcal Infections in Rabbits, abstracted, Federation Proc. **10**:332 (March) 1951.

8. Glaser, R. J.; Berry, J. W.; Loeb, L. H., and Wood, W. B.: The Effect of Cortisone on Bacterial Infections, abstracted, J. Clin. Invest. **30**:640-641 (June) 1951. White, R. G., and Marshall, A. H. E.: Effect of Cortisone on Pneumococcal Bacteremia, Preliminary Communication, Lancet **1**:891-892 (April 21) 1951.

9. Thomas, L.; Mogabgab, W. J., and Good, R. A.: The Effects of Cortisone on Experimental Bacterial Infections and on the Tissue Damage Produced by Bacterial Toxins, abstracted, J. Clin. Invest. **30**:678-679 (June) 1951.

10. Kass, E. H.; Ingbar, S. H.; Lundgren, M. H., and Finland, M.: The Effect of ACTH and Cortisone on Pneumococcal and Influenza Viral Infections in the White Mouse, J. Lab. & Clin. Med. **37**:780-788 (May) 1951.

11. Shwartzman, G.: Enhancing Effect of Cortisone upon Poliomyelitis Infection (Strain MEFI) in Hamsters and Mice, Proc. Soc. Exper. Biol. & Med. **75**:835-838 (Dec.) 1950. Southam, C. M., and Babcock, V. I.: Effect of Cortisone, Related Hormones, and Adrenalectomy on Susceptibility of Mice to Virus Infections, ibid. **78**:105-109 (Oct.) 1951.

12. Kilbourne, E. D., and Horsfall, F. L.: Lethal Infection with Coxsackie Virus of Adult Mice Given Cortisone, Proc. Soc. Exper. Biol. & Med. **77**:135-138 (May) 1951.

The drug did not influence the electrocardiographic changes associated with rheumatic fever and did not prevent complications.[13] According to Bayles, the usual doses of corticotropin and cortisone failed to cause durable remission in rheumatic disease.[14] Higher dosage, in amounts of 500 mg. of cortisone daily for 14 to 28 days, gave longer remissions. Symptomatic improvement occurred in five patients with viral hepatitis after doses of 100 mg. of corticotropin daily from 9 to 21 days.[15] The conditions of several patients with Hodgkin's disease were improved by cortisone therapy, which masked the symptoms, but septicemia developed.[16] Because brucellosis is characterized by granulomas in which Brucella may be protected against antibiotic agents used therapeutically and since cortisone inhibits granule formation, tests were made in infected animals treated with the hormone. However, cortisone converted hepatic granulomas into necrotic lesions, caused widespread disease, and increased the death rate.[17]

ANTIBIOTICS

No significant new facts were published on antibiotic therapy. The effects of several new agents were tested. Viomycin therapy successfully controlled tuberculosis established in guinea pigs with streptomycin-resistant tubercle bacilli.[18] Nine papers on the subject appeared in the January, 1951, issue of *The American Review of Tuberculosis.* Neomycin treatment had no demonstrable effect in patients with tuberculosis, but infection caused by Proteus bacilli and Gram-negative bacilli were favorably influenced. Ototoxic and nephrotoxic side-effects do not favor the use of neomycin.[19] Bacitracin and aureomycin were shown to be effective in the treatment of amebic colitis in 66% of cases.[20] Good results from bacitracin given intramuscularly were obtained in patients with lobar pneumonia, but its nephrotoxic effect precludes its use.[21] Several antifungal antibiotics were studied: fungicidin,[22] frequentin, and prodigiosin. Prodigiosin also is amebicidal.[23]

13. Hahn, E. O., and others: Effect of Cortisone on Acute Streptococcal Infections and Post-Streptococcal Complications, J. Clin. Invest. **30**:274-281 (March) 1951.

14. Bayles, T. B., and others: Significant Remissions in Rheumatic Diseases with High Dosage Cortisone Therapy, abstracted, J. Clin. Invest. **30**:628 (June) 1951.

15. Colbert, J. W.; Holland, J. F.; Heissler, I., and Knowlton, M.: The Use of ACTH in Acute Viral Hepatitis, New England J. Med. **245**:172-177 (Aug. 2) 1951.

16. Dubois-Ferrière, H.: Risk of Infection Associated with Prolonged Treatment with ACTH and Cortisone, Praxis **39**:974-975 (Nov. 9) 1950.

17. Abernathy, R.: The Effect of Cortisone on Experimental Brucellosis, abstracted, J. Clin. Invest. **30**:626 (June) 1951.

18. Karlson, A. G., and Gainer, J. H.: Viomycin in Tuberculosis of Guinea Pigs Due to Streptomycin-Sensitive and to Streptomycin-Resistant Tubercle Bacilli, Proc. Staff Meet., Mayo Clin. **26**:53-59 (Jan. 31) 1951.

19. Waisbren, B. A., and Spink, W. W.: A Clinical Appraisal of Neomycin, Ann. Int. Med. **33**:1099-1119 (Nov.) 1950.

20. Most, H.; Miller, J. W.; Grossman, E. B., and Conan, N.: Treatment of Amebiasis with Bacitracin, J. A. M. A. **143**:792-794 (July 1) 1950. Most, H.; Miller, J. W., and Grossman, E. B.: Treatment of Amebiasis with Bacitracin and Other Antibiotics, Am. J. Trop. Med. **30**:491-497 (July) 1950.

21. Reisner, E. H.; Bailey, F. M., and Appelbaum, E.: The Treatment of Pneumonia with Bacitracin, Ann. Int. Med. **34**:1232-1242 (May) 1951.

22. Hazen, E. L., and Brown, R.: Fungicidin, an Antibiotic Produced by a Soil Actinomycete, Proc. Soc. Exper. Biol. & Med. **76**:93-97 (Jan.) 1951.

23. Balamuth, W., and Brent, M. M.: Biological Studies on Entamoeba Histolytica: IV. Direct Action of the Antibiotic, Prodigiosin, Proc. Soc. Exper. Biol. & Med. **75**:374-378 (Nov.) 1950.

The sensitiveness of 20 newly isolated strains of gonococci was measured against penicillin, aureomycin, chloramphenicol, streptomycin, bacitracin, neomycin, polymyxin B (aerosporin®), polymyxin D, and sulfadiazine. On a weight basis penicillin was by far the most active, followed by aureomycin and chloramphenicol. Polymyxin and sulfadiazine gave the poorest results.[24]

Woods and his co-workers collected reports of 25 instances of moniliasis (Candida albicans) induced by therapy with penicillin, aureomycin, and chloramphenicol.[25] Monilial infection may involve the oropharynx and esophagus, the intestinal tract, and the lungs. Pulmonary moniliasis is the most serious. Fungi become prolific and invasive because competing bacteria are suppressed by the antibiotics. In the treatment of moniliasis, the authors apparently include the experimental procedure of specific vaccination against the fungus with the intention of causing desensitization and the administration of potassium iodide, a drug of unproved value.

Finland discussed the present status of antibiotics used for the treatment and prevention of infectious diseases.[26] While the prophylactic value of penicillin in meningococcic infections, rheumatic fever, and gonorrhea is apparent, it has not been so successful in preventing bacteremia after dental or oral surgical procedures and was unsuccessful in preventing infections of the respiratory tract. Facetiously, he alludes to the possible universal use of antibiotics prophylactically from the "womb to the tomb"; that is, beginning with the prevention of maternal or fetal infection at childbirth, then for prevention of the hazards of innumerable infections during life or their treatment, and finally for the prevention of terminal infection in old age. He apparently feels as I do that about 90% of antibiotics as now administered are wasted in overdosage and in treatment of diseases not affected by them. Except for special conditions, combinations of antibiotics rarely are of more value than single agents. Finland emphasizes the seriousness of the increasing number of infections caused by staphylococci resistant to penicillin. A new entity—staphylococcic dysentery—was encountered in patients during treatment with aureomycin or terramycin.

Kirby points out that many of the diseases on which aureomycin, chloramphenicol, and terramycin exert their most striking effects are relatively uncommon in the United States, as, for example, typhoid, psittacosis, tularemia, and rickettsioses.[27] Because of their greater cost they need not be employed for diseases controlled with penicillin, unless penicillin-resistant bacteria are operative or unless the patient is hypersensitive to penicillin. Furthermore, oral therapy with the newer antibiotics is less reliable, owing to irregularities of absorption in the gastrointestinal tract, and unpleasant side-effects are commoner than with penicillin therapy.

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24. Gocke, T. M.; Wilcox, C., and Finland, M.: Antibiotic Spectrum of the Gonococcus, Am. J. Syph. **34**:265-272 (May) 1950.

25. Woods, J. N.; Manning, I. H., and Patterson, C. N.: Monilial Infection Complicating the Therapeutic Use of Antibiotics, J. A. M. A. **145**:207-211 (Jan. 27) 1951.

26. Finland, M.: The Present Status of Antibiotics in Bacterial Infections, Bull. New York Acad. Med. **27**:199-220 (April) 1951.

27. Kirby, W. M. M.: Recent Trends in Antibiotic Therapy, J. A. M. A. **144**:233-236 (Sept. 16) 1950.

Domagk synthesized a number of sulfonamide compounds which are active against anaerobic microbes.[28] One called "supronal" (a mixture of sulfamerazine and "marbadal" [4-aminomethylbenzene-sulfonamide-sulfathiourate]) is said to surpass penicillin in its action against enterococci, shigellae, Pseudomonas aeruginosa, and Proteus vulgaris. Thiosemicarbazone, active against Mycobacterium tuberculosis, also influences the sedimentation rate of erythrocytes in rheumatic and neoplastic disease, and controls the symptoms as well.[29] The mechanism of its action is unknown. Several related compounds suppressed the extent of pulmonary lesions in rats infected with a pneumotropic virus.[30]

Penicillin.—According to Goldstein, John Tyndall observed the inhibiting effect on bacteria of a mold (Penicillium glaucum) in 1874, and Vuillemin coined the term antibiosis in 1889.[31] Penicillium glaucum was so named in 1809.

A comprehensive study by a large group of investigators led by Curtis gathered the accumulated experience in the treatment of syphilis in the eight years since penicillin first was used.[32] Penicillin alone far surpasses any other form of therapy. There is no longer any need for the use of heavy metals, either alone or in combination with penicillin. Various dosage forms for the different kinds and stages of syphilis are outlined in the report. There is no evidence to indicate a rapid eradication of syphilis in the population as a result of therapy with penicillin. At least another decade must elapse before the effect of therapy on the incidence of syphilis can be estimated.[33]

According to Reekie, unexplained fever and malaise after penicillin therapy for gonorrhea strongly suggest coexisting syphilis.[34] Syphilis may be masked or suppressed dangerously by inadequate dosage. Patients having such reaction must be studied carefully.

The serious problem of penicillin-resistant strains of staphylococci was discussed editorially.[35] Apparently the indiscriminate widespread use of penicillin is leading to the development of an increasing number of resistant strains. Persons who have never received penicillin may be infected with a strain which resists penicillin therapy and for which other antibiotics or ones as yet undiscovered must be used. French observers encountered staphylococci which are truly resistant to penicillin and others which produce penicillinase. From one patient, four strains were isolated and all secreted the enzyme. Therapy with penicillin in huge amounts

28. Two New Sulfonamide Compounds Introduced by Domagk, Foreign Letters, J. A. M. A. **144**:1019-1020 (Nov. 18) 1950.

29. Heilmeyer, L.: Nonspecific Action of Thiosemicarbazone, Beitr. Klin. Tuberk. **102**:583-585 (Feb. 9) 1950.

30. Eaton, M. D.; Perry, M. E., and Gocke, T. M.: Effect of Nitro-Compounds and Aldehyde Semicarbazones on Virus of Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **77**:422-425 (July) 1951.

31. Goldstein, H. I.: Errors of Priority Credit in Medicine, Rev. Gastroenterol. **17**:393-400 (May) 1950.

32. Curtis, A. C.: Penicillin Treatment of Syphilis, J. A. M. A. **145**:1223-1226 (April 21) 1951.

33. Moore, J. E.: An Evaluation of Public Health Measures for the Control of Syphilis, Am. J. Syph. **35**:135-140 (March) 1951.

34. Reekie, A. A. M.: The Danger of Penicillin Therapy in Gonorrhea, Lancet **1**:327-328 (Feb. 10) 1951.

35. Penicillin-Resistant Staphylococci, editorial, J. A. M. A. **145**:1268-1269 (April 21) 1951.

failed, but streptomycin treatment was curative. In another study, 38 of 300 pathogenic strains of staphylococci secreted penicillinase.[36] The importance of removing a focus of infection in the treatment of staphylococcic infection was illustrated in a patient whose disease resisted massive daily doses of penicillin (10,000,000 units), aureomycin (500 mg.), and dihydrostreptomycin (0.5 gm.) combined. Recovery occurred when an infected packing of oxidized cellulose and absorbable gelatin sponge (gelfoam®) was removed from the abdomen.[37]

In studies on the efficacy of oral therapy with penicillin, it was the conclusion of Bunn and his co-workers that satisfactory results were obtained with doses of 500,000 units given twice or thrice a day. For patients with bacterial endocarditis, meningitis, and staphylococcic sepsis, parenteral therapy is preferred.[38]

In infants and children with pneumonia, treatment with penicillin often caused the flora of the sputum to become composed only of Gram-negative bacteria. When such conversion occurred, the disease was of longer duration and more fatal. At necropsy, Gram-negative bacteria had invaded the lungs in several cases. In such instances other appropriate antibiotics must be used.[39]

Among 215 patients with dermatitis, a hypersensitive reaction to penicillin was the cause in 32. In each instance penicillin had been applied locally in the form of a lotion, dusting powder, or cream. There rarely is need for applying penicillin topically; other nonsensitizing therapy should be used, or penicillin should be injected parenterally.[40]

Penicillin therapy had no effect on the clinical course of infectious mononucleosis in a large controlled group of patients.[41]

A new form of penicillin, penicillin O, was introduced in the hope of providing a substitute for penicillin G if patients are hypersensitive to the latter. Unfortunately, hypersensitivity also develops to penicillin O. Penicillin O cannot safely be substituted in treatment of patients hypersensitive to the penicillin G preparation.[42] Another new form (benzyl penicillin-beta-diethylaminoethylester hydriodide) is said to have a predilection for pulmonary tissue, where it accumulates in

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36. Martin, R.; Chabbert, Y.; Sureau, B., and Demoures, C.: New Problems in Penicillin Therapy: Staphylococci Which Are Producing Penicillinase, Presse méd. **58**:197-198 (Feb. 25) 1950.

37. Krawitz, S., and Breed, C. N.: Staphylococcus Aureus Bacteremia: Report of a Case with Cure by Combined Antibiotic Therapy and Surgical Eradication of an Unusual Focus of Infection, J. A. M. A. **145**:819-821 (March 17) 1951.

38. Bunn, P., and others: Absorption and Clinical Use of Penicillin Preparations Given in Large Oral Doses, J. A. M. A. **144**:1540-1543 (Dec. 30) 1950.

39. Haffner, F. D.; Neter, E., and Rubin, M. I.: Penicillin and Its Effect in Producing a Predominant Gram-Negative Bacillary Flora in the Upper Respiratory Tract of Children, Pediatrics **6**:262-268 (Aug.) 1950.

40. Tzanck, A.; Sidi, E., and Gautard, J.: Risks of External Application of Penicillin, Presse méd. **59**:713-714 (May 23) 1951.

41. Bennike, T.: Penicillin Treatment of Infectious Mononucleosis: Comparison of Effects in 99 Patients With and in 67 Patients Without Penicillin Therapy, A. M. A. Arch. Int. Med. **87**:181-189 (Feb.) 1951.

42. Adair, C. V.; Woodin, W. G., and Bunn, P. A.: Clinical and Pharmacologic Studies with Allylmercaptomethyl Penicillin (Penicillin "O"), Am. J. Med. **11**:188-195 (Aug.) 1951. Siegal, S.: Allergy to Penicillin O and Management of Penicillin Hypersensitivity, ibid. **11**:196-201 (Aug.) 1951.

large amount after parenteral injection.[43] One wonders whether a resurrection of the idea of elective localization of a number of compounds is in store for various other organs as well.

Aureomycin.—According to Roth, aureomycin is the agent of choice to prevent bacteremia incident to the extraction of teeth. When given the day before, on the day of operation, and for a day afterward to 25 patients, bacteremia occurred in only 1, as compared with 14 in an untreated group.[44] Aureomycin therapy was said to be of prompt benefit in cases of abacterial pyuria [45] and viral pneumonia.[46] Aureomycin was used in treatment of pyuria because the drug is said to be effective in "viral" diseases. However, if by inference, psittacosis and lymphogranuloma venereum are meant, these are not true viral diseases. Shanks believes infantile diarrhea to be of viral origin because neither aureomycin nor chloramphenicol had any beneficial effects.[47] Of 45 patients with Q fever who received aureomycin, 32 became afebrile within five days. The rest were not benefited.[48]

Aureomycin administration had no effect on the common cold. It had no effect on infectious mononucleosis,[49] disseminated herpes simplex,[50] or herpes zoster [51] except to control secondary bacterial infection.

Chloramphenicol.—Therapy with chloramphenicol was successful in 12 cases of meningitis caused by Hemophilus influenzae.[52] The drug gave satisfactory results in almost all 160 patients with typhoid.[53] Because an average of four days elapses before symptoms are controlled by therapy with chloramphenicol, cortisone was used as an adjuvant to speed recovery. After combined therapy, the average period of illness was reduced to about two days. Two relapses occurred among eight patients, but whether cortisone was the cause is uncertain.[54] Relapse after

43. Jensen, K. A., and others: Leocillin (Benzyl Penicillin-Beta-Diethylaminoethylester Hydriodide), Acta path. et microbiol. scandinav. **28**:407-414, 1951.

44. Roth, O.; Cavallaro, A. L.; Parrott, R. H., and Celentano, R.: Aureomycin in Prevention of Bacteremia Following Tooth Extraction, Arch. Int. Med. **86**:498-504 (Oct.) 1950.

45. Baurys, W.: Abacterial Pyuria: Treatment with Aureomycin, J. A. M. A. **145**:403-404 (Feb. 10) 1951.

46. Schoenbach, E. B.; Sweed, A.; Tepper, B., and Bryer, M. S.: Evaluation of Aureomycin Therapy in Primary Atypical Pneumonia, New England J. Med. **243**:799-806 (Nov. 23) 1950.

47. Shanks, R. A.: Aureomycin and Chloramphenicol in Infantile Diarrhoea, Brit. M. J. **2**:272-275 (Aug. 4) 1951.

48. Clark, W. H.; Lennette, E. H., and Meiklejohn, G.: Q Fever in California: III. Aureomycin in Therapy of Q Fever, A. M. A. Arch. Int. Med. **87**:204-217 (Feb.) 1951.

49. Cronk, G. A.: Aureomycin in Infectious Mononucleosis: A Control Study, Am. J. M. Sc. **222**:413-416 (Oct.) 1951.

50. Buerck, M. S., and Blank, H.: Disseminated Herpes Simplex (Kaposi's Varicelliform Eruption) and Failure of Penicillin and Aureomycin to Influence Its Course, New England J. Med. **244**:670-672 (May 3) 1951.

51. Carter, A. B.: Investigation into Effects of Aureomycin and Chloramphenicol in Herpes Zoster, Brit. M. J. **1**:987-991 (May 5) 1951.

52. McCrumb, F. R., and others: Treatment of Hemophilus Influenzae Meningitis with Chloramphenicol and Other Antibiotics, J. A. M. A. **145**:469-474 (Feb. 17) 1951.

53. Furbetta, D., and Bufalari, A.: Clinical and Immunologic Aspects of the Course of Typhoid After Chloramphenicol Treatment, Sett. med. **39**:138-141 (March 15) 1951.

54. Smadel, J. E.; Ley, H. L., and Diercks, F. H.: Treatment of Typhoid Fever: I. Combined Therapy with Cortisone and Chloramphenicol, Ann. Int. Med. **34**:1-9 (Jan.) 1951.

therapy occurs as often as in untreated patients.[55] Variant strains of Klebsiella pneumoniae, either resistant to or dependent on chloramphenicol were observed.[56]

Terramycin.—The relative value of terramycin as compared with other antibiotics is not yet established. Its use appeared to be beneficial in about one-half of 19 patients with pneumococcic pneumonia, but in 5 administration of other antibiotics was necessary to bring about recovery. The response was favorable in six cases of nonpneumococcic pneumonia. Terramycin therapy was of no value in patients with pneumonia caused by a mixture of bacteria. Good results were obtained in only one-third of patients with infection of the urinary tract or whooping cough.[57] The agent had no effect on experimental influenza infection in mice. The conditions of several patients with influenza improved promptly after treatment with terramycin, but this might have occurred anyway.[58] Terramycin treatment successfully controlled syphilis induced in rabbits.[59]

Antibiotics in Combination.—There is a strong temptation in the treatment of serious disease to use every remedy likely to have a beneficial effect. Such procedure may be desirable at times, but it often is unnecessary and confuses the evaluation of any single antibiotic therapeutic agent. When dealing with an obscure diagnostic problem or if means are not available for making an etiologic diagnosis in an emergency, a combination of antibiotics effective against a wide variety of bacteria may be used. The matter of synergistic or additive value of one antibiotic in relation to another is not understood completely, and in certain instances antagonism may be demonstrated. For example, penicillin acts best as a bactericide when bacteria are growing and multiplying. If penicillin is combined with chloramphenicol, the latter, being bacteriostatic, stops the growth of bacteria and cancels the effectiveness of penicillin. Certain combinations of antibiotics, however, may be used to advantage. As shown by Hunter in experimental studies, streptomycin alone had no effect on a strain of nonhemolytic streptococci.[60] Penicillin alone killed many cocci but not all; however, a combination of the two agents sterilized the culture. Theoretically, a method of this sort should be effective in the treatment of subacute bacterial endocarditis caused by otherwise resistant nonhemolytic streptococci. The value of combined antibiotic therapy for brucellosis and other diseases is discussed elsewhere in this review.

Jawetz and his associates add further data on the antagonistic effects of penicillin and chloramphenicol.[61] The observations raise questions of the advisability of

55. Matteuci, W. V.; Schimmel, N. H., and Boger, W. P.: Typhoid Fever: Chloramphenicol Therapy and the Problem of Relapse, Am. J. M. Sc. **222**:446-451 (Oct.) 1951.

56. Gocke, T. M., and Finland, M.: Development of Chloramphenicol-Resistant and Chloramphenicol-Dependent Variants of a Strain of Klebsiella Pneumoniae, Proc. Soc. Exper. Biol. & Med. **74**:824-829 (Aug.) 1950.

57. Finland, M., and others: Clinical Studies on Terramycin, Ann. New York Acad. Sc. **53**:290-296 (Sept. 15) 1950.

58. Kass, E. H.; Barnes, M. W., and Finland, M.: Terramycin in Influenza Viral Infections, Ann. New York Acad. Sc. **53**:412-421 (Sept. 15) 1950.

59. Levaditi, C., and Vaisman, A.: Terramycin as a New Antisyphilitic Medication, Presse méd. **41**:849 (June 16) 1951.

60. Hunter, T. H.: Speculations on the Mechanism of Cure of Bacterial Endocarditis, J. A. M. A. **144**:524-527 (Oct. 14) 1950.

61. Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: Interference of Chloramphenicol with the Action of Penicillin, A. M. A. Arch. Int. Med. **87**:349-359 (March) 1951.

using combinations of certain antibiotics in therapy. According to Bunn, true interference of one agent with another was not observed in test-tube experiments.[62]

The knowledge of bacterial resistance to antibiotic agents and sulfonamide compounds was reviewed. Resistance can be acquired by most, if not all, species of bacteria at different rates and in different degree.[63]

INFECTIONS OF THE RESPIRATORY TRACT

The Common Cold.—In the Dunham lectures, Andrewes summarizes his observations, views, and knowledge in general of viruses, of influenza, and of the common cold.[64] One experiment is of particular interest: A small container of fluorescin in a viscous fluid is attached to a person's nose. Shortly after blowing his nose, ultraviolet rays reveal fluorescin to be spread over the face and hands, and "all over the room in fact, even on to the food he or his companion is about to eat." The point is that a person with a cold who blows his nose spreads virus-laden secretion more widely than is generally believed.

In spite of much evidence to the contrary, Kerr still does not regard the common cold as a contagious disease spread by ordinary human contact.[65] He believes that physiologic mechanisms are involved which have to do with adjustment to cooling and to irritating factors. According to Andrewes, who has conducted extensive research on the subject, a virus causes the common cold "and everything we have seen confirms that opinion." Bloomfield writes that "no serious student of the common cold problem now doubts that the essential cause is a filtrable virus."[66] He also deplores the widespread practice of treating colds with various antibiotic agents which have no influence on colds. According to Downs, irradiating the air with ultraviolet light failed to influence the number of infections of the respiratory tract in controlled studies in several schools.[67]

Andrewes and his co-workers kept 12 volunteers in strict isolation on an island for 10 weeks to permit them, if possible, to lose any immunity they may have had to "colds."[68] At the end of that time the volunteers were divided into three groups of four each. The first group was exposed to "indirect" contact by entering a room and handling objects previously contaminated by six persons who had active colds induced by inoculation with cultivated virus; the second group was

62. Bunn, P. A.: Combined Antimicrobial Action upon Penicillin Resistant Organisms in Vitro, abstracted, J. Clin. Invest. **30**:631 (June) 1951.

63. Miller, C. P., and Bohnhoff, M.: The Development of Bacterial Resistance to Chemotherapeutic Agents, in Annual Review of Microbiology, edited by C. E. Clifton, S. Raffel, and H. A. Barker, Stanford, Calif., Annual Reviews, Inc., 1950, Vol. 4, pp. 201-222. Miller, C. P.: New Problems in the Treatment of Infectious Disease, Ann. Int. Med. **35**:763-770 (Oct.) 1951.

64. Andrewes, C. H.: Adventures Among Viruses: I. Some Properties of Viruses, New England J. Med. **243**:161-166 (Feb. 2) 1950; II. Epidemic Influenza, ibid. **243**:197-203 (Feb. 9), 1950; III. The Puzzle of the Common Cold, ibid. **243**:235-240 (Feb. 16), 1950.

65. Kerr, W. J.: The Common Cold and Its Implications, Ann. Int. Med. **33**:333-345 (Aug.) 1950.

66. Bloomfield, A. L.: Some Problems of the Common Cold, J. A. M. A. **144**:287-292 (Sept. 23) 1950.

67. Downs, J.: Control of Acute Respiratory Illness by Ultraviolet Lights, Am. J. Pub. Health **40**:1512-1520 (Dec.) 1950.

68. Andrewes, C. H.; Lovelock, J. E., and Sommerville, T.: An Experiment on the Transmission of Colds, Lancet **1**:25-27 (Jan. 6) 1951.

exposed to air-borne infection by remaining in a room with six persons with colds but separated from them by a curtain; the third group had direct contact with persons with colds. Surprisingly, none of the volunteers contracted colds. The negative results seem to confirm the idea of Kerr that colds are not viral in origin or contagious. But, because of the unsuccessful experiments after exposure to patients with induced colds, four volunteers were then exposed for three to eight hours to a person with a cold acquired naturally. Of these volunteers, three contracted colds three or four days later. Evidently, either 10 weeks is not long enough to lose immunity to colds or "natural" colds are more easily transmitted than colds induced with cultivated virus.

In a controlled study, Buchan and his co-workers found that the traditionally used APC tablet (acetylsalicylic acid-acetophenetidin-caffeine compound) gave no more symptomatic relief than did placebo tablets.[69]

Ward and Proctor succeeded in propagating virus of the common cold obtained from a patient through five passages in chick embryos.[70] By instilling cultures intranasally, typical colds developed in 61% of 23 volunteers. No symptoms of a cold appeared in 24 other volunteers who received autoclaved culture and normal allantoic fluid. Andrewes informs me of his success in causing colds in volunteers with cultures of Ward's WW virus. Unfortunately, the virus soon was lost in passage in eggs. A method for the detection of growth of the virus in chick embryos is under study.[70] It is based on a procedure using radioactive phosphorus and probably depends on an alteration in the metabolism of phosphorus in virus-infected embryos. The test may prove of value in the study of other viruses as well, particularly those which cause pneumonia, hepatitis, and dysentery.

An epidemic of a peculiar disease of unknown cause occurred in Louisiana in November, 1950.[71] About 300 cases were observed of disease of the upper respiratory tract, with fever, headache, irritability, abdominal pain, splenomegaly, and hepatomegaly. In a few patients, there were general swelling of lymph nodes and a measles-like rash of vesicular lesions. The leucocyte count usually ranged between 15,000 and 20,000.

Influenza.—Unnecessary alarm arose in the winter of 1951 from reports in newspapers of a serious epidemic of influenza in England. Influenza was widespread but mild in England in December, and a number of deaths among old persons occurred. Mild epidemics, not unusual in nature, caused by viruses of Types A and A′ occurred in the United States.[72] Studies of the 1950 outbreak of influenza in the United States revealed the presence of strains of influenza A virus which are antigenically different from strains recovered in epidemics in

69. Buchan, R. F.; Gras, A. E., and David, F. H.: Symptomatic Treatment of the Common Cold, A. M. A. Arch. Indust. Hyg. **4**:32-42 (July) 1951.

70. Ward, T. G., and Proctor, D. F.: Isolation of a Common Cold Virus in Chick Embryos and the Clinical Manifestation It Produces in Human Volunteers, Am. J. Hyg. **52**:91-106 (July) 1950. Ward, T. G.: The Use of Radioactive Phosphorus in Studies of Chick Embryo Infections with a Common Cold Virus, ibid. **52**:107-132 (July) 1950.

71. Upper Respiratory Diseases—Cause Undetermined, Report of Epidemics, Pub. Health Rep. **66**:82 (Jan. 19) 1951.

72. Scheele, L. A.: Influenza Epidemic in Great Britain and Europe, Correspondence, J. A. M. A. **145**:344 (Feb. 3) 1951.

previous years.[73] A progressive and continuous change seems to have occurred which necessitates a replacement of the older strains used for vaccines and diagnostic antigens with the new ones. In a study of 252 patients in an epidemic of influenza A′ in a military group, Kilbourne and Loge found no clinical differences from influenza caused by A or B influenza virus.[74] Influenza, as believed generally, is primarily an infection of the upper part of the respiratory tract. Gastrointestinal symptoms rarely caused complaint, and pneumonia was detected in only 2 of 76 patients studied in detail.

Andrewes and his co-workers summarized information on the European epidemic of 1948.[75] They urge investigators in all countries to adopt a uniform system for the designation of strains. Newly isolated viruses should be sent to a central laboratory for identification. In preparation they should be "freeze-dried" immediately after isolation to prevent biologic variation and subsequent confusion in classification. To avoid misunderstanding, an international committee formulated standardized methods for the diagnosis of influenza.[76]

Still more variants of influenza A virus are reported.[77] In an epidemic in Baltimore caused by influenza virus A′, five new strains were isolated. They were related to other A and A′ strains, yet were different antigenically and were pneumotropic for mice on direct inoculation without previous passage. They have not yet been named. Tamm and his associates found variants among influenza B viruses.[78] Vaccine prepared against one variant failed to protect against infection with another. One may predict the isolation of more variants and even of new types.

Francis and his associates isolated another influenza virus called influenza C.[79] It was obtained from a patient with signs and symptoms characteristic of influenza during an epidemic of influenza A in the spring of 1950. Antibodies for the virus were found to be widely distributed in the population. The virus was serologically and immunologically distinct from other strains of influenza virus and was not related to the viruses of other common infectious diseases.

A new system was proposed for the designation of antigenic components of influenza A, B, and C viruses.[79a] The scheme appears to be as complicated as the

73. Ward, T. G., and Eddy, B. E.: An Antigenically Distinct Subtype of Influenza Virus A Which Is Virulent for Mice in Primary Passage of Allantoic Fluid, Science **112**:501-503 (Oct. 27) 1950.

74. Kilbourne, E. D., and Loge, J. P.: Influenza A Prime: A Clinical Study of an Epidemic Caused by a New Strain of Virus, Ann. Int. Med. **33**:371-379 (Aug.) 1950.

75. Chu, C. M.; Andrewes, C. H., and Gledhill, A. W.: Influenza in 1948-1949, Bull. World Health Organ. **3**:187-214, 1950.

76. Committee on Standard Serological Procedures in Influenza Studies: An Agglutination-Inhibition Test Proposed as a Standard of Reference in Influenza Diagnostic Studies, J. Immunol. **65**:347-353 (Sept.) 1950.

77. Hilleman, M. R.; Mason, R. P., and Rogers, N. G.: Laboratory Studies on the 1950 Outbreak of Influenza, Pub. Health Rep. **65**:771-777 (June 16) 1950.

78. Tamm, I.; Kilbourne, E. D., and Horsfall, F. L.: Comparison of Influenza B Virus Strain from the 1950 Epidemic with Strains of Earlier Epidemics, Proc. Soc. Exper. Biol. & Med. **75**:89-92 (Oct.) 1950.

79. Francis, T.; Quilligan, J. J., and Minuse, E.: Identification of Another Epidemic Respiratory Disease, Science **112**:495-497 (Oct. 27) 1950.

79a. Hilleman, M. R.: System for Measuring and Designating Antigenic Components of Influenza Viruses with Analysis of Recently Isolated Strains, Proc. Soc. Exper. Biol. & Med. **78**:208-215 (Oct.) 1951.

one now used to classify Shigella and Salmonella. It is helpful in detecting progressive variability of strains of virus and for their accurate classification. A sample formula of the WS strain for instance is $Aa_3b_1c_0d_0$.

In a previous report by Finland and his co-workers, aureomycin was thought to have caused rapid improvement in a number of cases of severe influenza. However, a controlled study under Meiklejohn's direction during an epidemic of influenza A′ showed no difference in patients treated with aureomycin and those given penicillin, as compared with patients receiving no therapy at all.[80] Nor did either aureomycin or terramycin have any protective effect against the toxic action of influenza virus in mice.[81]

A rapid method for the detection of influenza virus in throat washings during epidemics is described.[82] It consists of concentrating and eluting the virus by absorption on red cells, then neutralizing with specific antiserums. With this test, diagnosis can be made within a day. By high-power microscopy it is possible to visualize particles which resemble the virus of influenza as it resides in tissues.[83] The virus particles appeared to be arranged in clusters as if they developed from the walls of the alveolar cells and grew at the expense of the cytoplasm of the infected cells.

Burnet summarizes his views on influenza virus in a series of papers in the February, 1951, issue of the *Bulletin of the Johns Hopkins Hospital.*

OTHER VIRAL DISEASES

Poliomyelitis.—At least 9 of 10 persons over the age of 15 have naturally acquired antibodies against the virus of poliomyelitis.[84] Studies indicate that every year about 20% of children become infected with the Lansing type of poliomyelitis virus, the vast majority with inapparent infection. A second attack of poliomyelitis which was fatal was reported with necropsy study.[85]

An editorial deals with several reports from England in which immunization procedures against diphtheria and whooping cough performed at a time that poliomyelitis was epidemic seemed to render the paralysis of poliomyelitis severer in the extremity used for vaccination.[86] If there is a relationship, it is just as important not to immunize children at a time that poliomyelitis is likely to be epidemic as it is to avoid tonsillectomy. In experimental studies the incubation

80. Thalmann, W. G.; Kempe, C. H.; Worrall, J. A., and Meiklejohn, G.: Aureomycin in the Treatment of Influenza: A Controlled Study, J. A. M. A. **144**:1156-1157 (Dec. 2) 1950.

81. Kass, E. H.; Lundgren, M. M., and Finland, M.: Failure of Aureomycin and Terramycin to Increase Resistance to Toxic Action of Influenza Virus, Proc. Soc. Exper. Biol. & Med. **75**:520-523 (Nov.) 1950.

82. Kalter, S. S.: A Rapid Method for Detection of Influenza Virus During Epidemics, Proc. Soc. Exper. Biol. & Med. **74**:607-608 (July) 1950.

83. Eddy, B. E., and Wyckoff, R. W. G.: Influenza Virus in Sectional Tissues, Proc. Soc. Exper. Biol. & Med. **75**:290-293 (Oct.) 1950.

84. Poliomyelitis: Nine of 10 Persons Carry Polio Antibodies, abstracted, Pub. Health Rep. **65**:1681-1682 (Dec. 15) 1950.

85. Hoyne, A. L., and Lipton, I.: Second Attacks of Poliomyelitis: Report of a Case with Autopsy Findings, J. A. M. A. **146**:707-709 (June 23) 1951.

86. Poliomyelitis and Prophylactic Immunization, editorial, J. A. M. A. **143**:240-241 (Sept. 16) 1950.

period of poliomyelitis [87] and encephalomyelitis [88] was significantly shortened in mice given injections of pertussis vaccine or diphtheria toxoid, as compared with unvaccinated mice. In other studies, the application of poliomyelitis virus to the pharynx of monkeys prior to tonsillectomy was followed regularly by bulbar paralysis. When tonsillectomy was not done, spinal paralysis usually resulted.[89]

A similar circumstance may pertain in patients in whom rheumatic fever is reactivated by smallpox vaccination.[90] During the smallpox alarm in New York city in 1947 when thousands of persons were vaccinated, several instances of rheumatic fever apparently were precipitated by vaccination. German clinicians report on four patients in whom tuberculous meningitis developed 12 days to 8 weeks after immunization with antityphoid vaccine.[91] Children, they say, should not be vaccinated if the tuberculin reaction is positive or if evidence of tuberculosis is present.

Women are unusually susceptible to poliomyelitis in the third trimester of pregnancy.[92] Spontaneous abortion occurs in 35% of those who contract the disease, but deliberate interference with pregnancy is indicated only in bulbar poliomyelitis. The over-all mortality rate is about 13%. According to Ingalls and Aycock, infection of the upper respiratory tract may favor the development of poliomyelitis, especially during epidemics of the latter disease.[93]

Conflicting reports appeared concerning the effect of exercise on the severity of poliomyelitis. In one study deaths and severe disease in children were not related to the degree of physical activity either shortly before the onset of illness or at any time during it.[94] Age was a major factor. Adults were affected more seriously. In the other study, transportation over long distances during the disease seemed to be harmful and increased the fatality rate.[95]

87. Milzer, A.; Weiss, M., and Vanderboom, K.: Effect of Pertussis, Diphtheria Toxoid and Salmonella Immunization on Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **77**:485-488 (July) 1951.

88. Dean, D. J.; Cohen, S. M., and Dalldorf, G.: The Effect of Unrelated Vaccines on the Localization of Paralysis in Mouse Encephalomyelitis, Proc. Soc. Exper. Biol. & Med. **77**:834-836 (Aug.) 1951.

89. Faber, H. K.; McNaught, R. C.; Silverberg, R. J., and Dong, L.: Experimental Production of Post-Tonsillectomy Bulbar Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **77**:532-534 (July) 1951.

90. Freud, P.; Rook, G. D., and Brunhofer, A.: Reactivation of Rheumatic Fever by Smallpox Vaccination, J. Pediat. **36**:635-640 (May) 1950.

91. Auersbach, K., and von Bergmann, I.: Tuberculous Meningitis After Immunization Against Typhoid, Ztschr. klin. Med. **145**:346-350 (Sept. 9) 1950.

92. Horn, P.: Pregnancy Complicated by Anterior Poliomyelitis: Experience in Los Angeles County Hospital and Report of 180 Consecutive Cases, Ann. West. Med. & Surg. **5**:93-98 (Feb.) 1951.

93. Ingalls, T. H., and Aycock, W. L.: Upper-Respiratory Infection as a Factor Influencing Susceptibility to Poliomyelitis, New England J. Med. **245**:197-203 (Aug. 9) 1951.

94. Albrecht, R. M., and Locke, F. B.: Effect of Physical Activity on Prognosis of Poliomyelitis, J. A. M. A. **146**:769-771 (June 30) 1951.

95. Brahdy, M. B., and Katz, S. H.: Effect of Transportation on Severity of Acute Poliomyelitis, J. A. M. A. **146**:772-774 (June 30) 1951.

A report on 362 cases in the 1948 epidemic in North Carolina contains much information of practical value about the management of cases.[96] Five cases of encephalitis caused by the viruses of St. Louis and of western equine encephalitis occurred during an epidemic of poliomyelitis in Texas.[97]

According to Syverton and Fischer, the cockroach, after being fed material containing the virus of mouse encephalomyelitis, carried the virus for several days.[98] The insect, therefore, may serve as a natural carrier of viruses of the polio-encephalomyelitis group.

The virus of poliomyelitis injures and kills cells, as indicated by studies in flask cultures of tissues, but the addition of type-specific immune serum prevents a harmful effect.[99] Evidently the virus can multiply in cells in vitro. Its action on living cells may provide a measurement for the qualitative assay of virus, for the "typing" of it, and for the evaluation of the effect of possible therapeutic agents. Improvements in the method of preparing antigens also may provide a satisfactory diagnostic complement-fixing test.[100] Poliomyelitis virus grows well in tissue cultures of human testicular tissue.[101] In Bodian's studies, gamma globulin injected intramuscularly reduced the paralytic rate in monkeys inoculated with several poliomyelitis viruses.[102]

An epidemic of nearly 500 cases of a poliomyelitis-like disease occurred in the winter of 1948-1949 in Iceland.[103] There was paralysis in 28% of patients, but no deaths were reported. The incidence was high in adults, especially those between the ages of 15 and 19, and low in those less than 5 years old. Tests of only four samples of feces did not reveal the presence of either poliomyelitis virus or Coxsackie virus. Either virus may have been implicated in the epidemic despite these few negative results, but it is possible that some agent still unknown was operative.

Coxsackie Disease.—A symposium on the Coxsackie virus problem is in the September, 1950, issue of the *Federation Proceedings,* and the subject is reviewed editorially in the January, 1951, issue of the *Annals of Internal Medicine.* There are two groups of virus, A and B. Virus A causes lesions only of skeletal muscles in young mice. B virus is associated with most outbreaks of disease. There appear to be at least seven types of B virus. The viruses are said to cause symptoms of

96. Shutkin, N. M.: Clinical Notes on an Epidemic of Poliomyelitis, Ann. Int. Med. **34**:655-668 (March) 1951.

97. Dravin, I.; Coffey, J. H., and Dine, W. C.: Virus Encephalitis During a Poliomyelitis Epidemic: A Report of 5 Cases, Ann. Int. Med. **34**:705-711 (March) 1951.

98. Syverton, J. T., and Fischer, R. G.: The Cockroach as an Experimental Vector of the Virus of Spontaneous Mouse Encephalomyelitis (Theiler), Proc. Soc. Exper. Biol. & Med. **74**:296-298 (May) 1950.

99. Robbins, F. C.; Enders, J. F., and Weller, T. H.: Cytopathogenic Effect of Poliomyelitis Virus in Vitro on Human Embryonic Tissues, Proc. Soc. Exper. Biol. & Med. **75**:370-374 (Nov.) 1950.

100. Casals, J., and Olitsky, P. K.: A Complement-Fixation Test for Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **75**:315-318 (Nov.) 1950.

101. Smith, W. M.; Chambers, V. C., and Evans, C. A.: Growth of Neurotropic Viruses in Extraneural Tissues: IV. Poliomyelitis Virus in Human Testicular Tissues in Vitro, Proc. Soc. Exper. Biol. & Med. **76**:696-700 (April) 1951.

102. Bodian, D.: Prevention of Paralytic Poliomyelitis in Monkeys with Human Immune Globulin, Federation Proc. **10**:402-403 (March) 1951.

103. Sigurdsson, B., and others: A Disease Epidemic in Iceland Simulating Poliomyelitis, Am. J. Hyg. **52**:222-238 (Sept.) 1950.

protean nature, as, for example, headache, abdominal pain, backache, nasal obstruction, pain in the chest and cough, splenomegaly, abdominal tenderness, vesicular stomatitis, vomiting, and pain in the eyes, which, respectively, are outstanding symptoms or signs in different patients.

According to Huebner and his group, who studied an outbreak of possible Coxsackie disease, the view that the virus presumably causes disease of diverse nature may indicate that the virus itself plays little or no role; other diseases may be prevalent and Coxsackie virus may be a mere commensal.[104] The virus was recovered from two healthy persons, and specific neutralizing antibodies were demonstrated in the serums of 77% of 150 persons in the community studied. On the other hand, evidence of an acute infection in six laboratory workers who handled the virus strongly indicates its potential pathogenicity.[105] The symptoms were abdominal and thoracic pain, with evidence of meningeal involvement. The tendency to call Coxsackie virus "C" virus will cause appellative confusion with the newly isolated influenza C virus.

Bornholm disease, or epidemic myalgia, was recognized in Scandinavian countries for two decades and more recently in England. It may mimic other diseases, especially pleurodynia, nonparalytic poliomyelitis, coronary thrombosis, and appendicitis. A relationship or identity of Coxsackie disease with pleurodynia or Bornholm disease was suggested by Findlay and Howard.[106] Serum from patients with Bornholm disease in England fixed complement with Coxsackie Type 2 virus, and a virus resembling Coxsackie virus was isolated from a patient with Bornholm disease.

An attempt to isolate a virus from patients with epidemic pleurodynia in Boston failed in 1947. After the discovery of Coxsackie viruses, recourse was made to patients' throat washings which were preserved since 1947. By applying the proper technique, four strains of virus were recovered, two of which were antigenically related to a strain of Coxsackie virus. Although a rise in specific neutralizing antibodies against the new virus was demonstrated in other patients with pleurodynia, the puzzle still remains whether the virus actually caused the disease.[107] Melnick and Kaplan demonstrated antibodies against both Coxsackie virus and poliomyelitis virus in the serum of patients from whose stools both viruses were recovered during an epidemic of poliomyelitis.[108]

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104. Huebner, R. J.; Armstrong, C.; Beeman, E. A., and Cole, R. M.: Studies of Coxsackie Virus: Preliminary Report on Occurrence of Coxsackie Virus in a Southern Maryland Community, J. A. M. A. **144**:609-612 (Oct. 21) 1950.

105. Shaw, E. N.; Melnick, J. L., and Curnen, E. C.: Infections of Laboratory Workers with Coxsackie Viruses, Ann. Int. Med. **33**:32-40 (July) 1950.

106. Findlay, G. M., and Howard, E. M.: Coxsackie Viruses and Bornholm Disease, Brit. M. J. **1**:1233-1236 (May 27) 1950.

107. Weller, T. H.; Enders, J. F.; Buckingham, M., and Finn, J. J.: The Etiology of Epidemic Pleurodynia: A Study of 2 Viruses Isolated from a Typical Outbreak, J. Immunol. **65**:337-346 (Sept.) 1950.

108. Melnick, J. L., and Kaplan, A. S.: Dual Antibody Response to Coxsackie and Poliomyelitis Virus in Patients with Paralytic Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **74**:812-815 (Aug.) 1950.

Huebner and his co-workers described an outbreak of an infectious disease called herpangina by Zahorsky in 1924.[109] It involves children chiefly and seems to be spread by close contact in the summer months. The disease is characterized by fever, vomiting, prostration, and vesicles and ulcers in the oropharynx and lasts several days. It was believed by some to be caused by herpes virus, but a different virus was regularly isolated from the pharynx and stools of patients. The virus or group of viruses falls into the A group of Coxsackie viruses and is presumably the cause of herpangina. Coxsackie virus may be transmitted by cockroaches.[110]

Other undelineated conditions appear from time to time as "new" diseases. They usually are mild and often are overlooked. A case in point is described in Denmark of an acute disease characterized by dizziness, nystagmus, segmental neuritic pain, myositis, and vague visual disturbance, chiefly in adults.[111] It lasts one to several weeks. Most cases are mild.

Encephalitis.—During an epidemic of encephalitis in the summer of 1949 in North Dakota, the viruses of western equine encephalitis and poliomyelitis were identified in some cases, but in the majority the cause was unknown.[112] Evidently another unidentified neurotropic virus exists.

The virus of western equine encephalomyelitis was isolated from blackbirds, magpies, and mites found in an English sparrow's nest.[113] The eastern type of encephalomyelitis virus was isolated from a grackle.[114]

The virus of keratoconjunctivitis, which appeared in epidemic form in 1942, appears to be related to the virus of St. Louis encephalitis.[115] Another neurotropic virus, Ntaya virus, was discovered in mosquitoes, and it, in addition to the seven or eight others found in Africa and South America, is presently being studied.[116] Although infection with the virus of Japanese B encephalitis in animals had been noted previously, Burns now shows that pigs may be involved.[117] A congenital

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109. Huebner, R. J., and others: Herpangina: Etiological Studies of a Specific Infectious Disease, J. A. M. A. **145**:628-633 (March 3) 1951.

110. Fischer, R. G., and Syverton, J. T.: The Cockroach as an Experimental Vector of Coxsackie Virus, Am. J. Trop. Med. **31**:238-242 (March) 1951.

111. Rasmussen, O.: Question of "New" Epidemic Disease with Polymorphous Clinical Picture, Ugesk. læger **112**:802-804 (June 1) 1950.

112. Wenner, H. A., and others: Encephalitis in the Missouri River Basin: II. Studies on a Focal Outbreak of Encephalitis in North Dakota, Pub. Health Rep. **66**:1075-1085 (Aug. 24) 1951.

113. Sooter, C. A.; Howitt, B. F.; Gorrie, R., and Cockburn, T. A.: Encephalitis in Midwest: IV. Western Equine Encephalomyelitis Virus Recovered from Nestling Wild Birds in Nature, Proc. Soc. Exper. Biol. & Med. **77**:393-394 (July) 1951. Miles, V. I.; Howitt, B. F.; Gorrie, R., and Cockburn, T. A.: Encephalitis in Midwest: V. Western Equine Encephalomyelitis Virus Recovered from Mites Dermanyssus Americanus Ewing, ibid. **77**:395-396 (July) 1951.

114. Kissling, R. E.; Rubin, H.; Chamberlain, R. W., and Eidson, M. E.: Recovery of Virus of Eastern Equine Encephalomyelitis Virus from Blood of a Purple Grackle, Proc. Soc. Exper. Biol. & Med. **77**:398-399 (July) 1951.

115. Ruchman, I.: Relationship Between Epidemic Keratoconjunctivitis and St. Louis Encephalitis Viruses, Proc. Soc. Exper. Biol. & Med. **77**:120-125 (May) 1951. Cheever, F. S.: A Possible Relationship Between Viruses of St. Louis Encephalitis and Epidemic Keratoconjunctivitis, ibid. **77**:125-129 (May) 1951.

116. Smithburn, K. C., and Haddow, A. J.: Ntaya Virus: A Hitherto Unknown Agent Isolated from Mosquitoes Collected in Uganda, Proc. Soc. Exper. Biol. & Med. **77**:130-133 (May) 1951.

117. Burns, K. F.: Congenital Japanese B Encephalitis Infection of Swine, Proc. Soc. Exper. Biol. & Med. **75**:621-625 (Nov.) 1950.

disease in piglets said to be analogous to toxoplasmosis was described. The sow apparently was healthy, but the central nervous system of the offspring was severely affected.

Mumps.—In a series of papers on the prevention of mumps published in the May, 1951, issue of *The Journal of Immunology,* Henle and her co-workers reported on tests of the value of vaccine composed of inactivated or attenuated mumps virus, given intradermally or subcutaneously or sprayed into the mouth. The application of the skin test by intradermal injection did not give protection. Subcutaneous injection of vaccine caused transitory immunity. Oral spraying of "attenuated" virus caused mild signs of infection in 6 of 410 susceptible children. Four children vaccinated orally were exposed to mumps three months later without becoming infected, while four of six unvaccinated ones acquired mumps. The presence of a complement-fixing antibody or skin reactivity almost always indicated resistance to mumps.

Smallpox.—To account for the development of smallpox in persons apparently adequately vaccinated and supposedly immune, Benenson points out that the interpretation of the results of vaccination may be wrong.[118] The immediate reaction to smallpox vaccine is not evidence of immunity but a manifestation of hypersensitivity to fractions of virus. The reaction may follow an inoculation of dead, nonimmunizing virus. To avoid error in ascertaining the presence or absence of vaccine-induced immunity, the term "immune reaction" should be substituted by "immediate reaction." Immune and hyperergic reactions are the same morphologically. An immediate reaction indicates immunity only if the vaccine used is of known high potency.

Feulgen's method of applying desoxyribonucleic acid to scrapings on slides made from deep lesions of smallpox is said to provide a simple method for the diagnosis of smallpox.[119] The procedure differentiates virus particles from extraneous material.

Smallpox almost has been eradicated from this country.[120] Only 41 cases were reported in 1950. Nevertheless, vigilance must not be relaxed in regard to vaccination.

Pinkerton discusses the morphology of inclusions in cells associated with viral infections and lists those diseases in which inclusions are helpful in diagnosis and those in which inclusions have not been found.[121] Inclusions caused by chemical agents seldom cause confusion. Ayres and Feemster published an extensive informative discussion of serologic tests and their value for the diagnosis of many infectious diseases.[122]

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118. Benenson, A. S.: Immediate (So-Called "Immune") Reaction to Smallpox Vaccination, J. A. M. A. **143**:1238-1240 (Aug. 5) 1950.

119. Wolman, M.: Application of the Feulgen Reaction to the Laboratory Diagnosis of Smallpox, Proc. Soc. Exper. Biol. & Med. **74**:85-87 (May) 1950.

120. Smallpox Conquered but Still a Threat, Statist. Bull. Metrop. Life Insur. Co. **32**:8-10 (Feb.) 1951.

121. Pinkerton, H.: The Morphology of Viral Inclusions and Their Practical Importance in the Diagnosis of Human Disease, Am. J. Clin. Path. **20**:201-207 (March) 1950.

122. Ayres, J. C., and Feemster, R. F.: Serologic Tests in Diagnosis of Infectious Diseases, New England J. Med. **243**:996-999 (Dec. 21); 1034-1037 (Dec. 28) 1950.

DISEASES PROBABLY OF VIRAL ORIGIN

The subject of viral myocarditis was reviewed elsewhere.[123]

Hepatitis.—Two approaches were made to the problem of the relationship between viral hepatitis and cirrhosis or atrophy of the liver. In one, the records of patients who had hepatic atrophy or cirrhosis were reviewed to determine whether viral hepatitis was the inciting factor.[124] Among 130 cases of atrophy of liver, historical evidence of a previous attack of viral hepatitis was found in 36. Perkins, therefore, concludes that viral hepatitis is not an uncommon cause. In the other approach, a study was made of 114 patients who had had viral hepatitis 7 to 70 months previously to determine the incidence of sequels.[125] Most patients had recovered completely. Four patients had severe disabling hepatic disease, but most of the 44 who had continued disturbance complained of persistent or recurrent jaundice. Jaundice may occur when no lesion in the liver can be seen microscopically in tissue removed for biopsy. As pointed out before, the course of chronic hepatic disease incited by viral hepatitis in a way is analogous with chronic glomerulonephritis. Viral hepatitis may be transmitted by tattooing [126] and occurs also in drug addicts who use unsterile hypodermic instruments.[127]

Eight patients with serum hepatitis died within 3 to 13 days from the onset.[128] Necropsy studies were made on six. Ten other patients are mentioned in whom jaundice developed after the injection of irradiated plasma and whole blood. Irradiation was believed to destroy the virus of hepatitis and render plasma safe for use in therapy. However, in three papers published in the Sept. 16, 1950, issue of *The Journal of the American Medical Association,* a number of instances are reported in which hepatitis followed the injection of irradiated plasma; two deaths occurred. Evidently, a more efficient procedure must be devised. The usual method of preservation of blood and its constituents, namely, lyophilization and refrigeration, is favorable to the survival of any virus. To kill the virus, Allen and his many co-workers allowed plasma to stand at 78 to 96 F. for 3 to 12 months.[129] Storage apparently did not alter the value of the plasma or cause added untoward reactions when it was used in therapy. None of 212 patients who received the stored plasma acquired hepatitis.

Serum jaundice may be contracted by the laboratory personnel of a "blood bank." [130] Sixteen cases were recognized in four Memphis hospitals in three years.

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123. Myocarditis in Poliomyelitis and Related Viral Infections, editorial, Ann. Int. Med. **34**:1502-1508 (June) 1951.

124. Perkins, R. F.; Baggenstoss, A. H., and Snell, A. M.: Viral Hepatitis as a Cause of Atrophy and Cirrhosis of the Liver, Proc. Staff Meet., Mayo Clin. **25**:287-298 (May 24) 1950.

125. Post, J.; Gellis, S., and Lindenauer, H. J.: Studies on the Sequelae of Acute Infectious Hepatitis, Ann. Int. Med. **33**:1378-1397 (Dec.) 1950.

126. Smith, B. F.: Occurrence of Hepatitis in Recently Tattooed Service Personnel, J. A. M. A. **144**:1074-1076 (Nov. 25) 1950.

127. Steigmann, F.; Hyman, S., and Goldbloom, R.: Infectious Hepatitis (Homologous Serum Type) in Drug Addicts, Gastroenterology **15**:642-646 (Aug.) 1950.

128. Runyan, J.; Wright, A. M., and Beebe, R. T.: Homologous Serum Jaundice: Report of 8 Fatal Cases, J. A. M. A. **144**:1065-1068 (Nov. 25) 1950.

129. Allen, J. G., and others: Homologous Serum Jaundice and Its Relation to Methods of Plasma Storage, J. A. M. A. **144**:1069-1074 (Nov. 25) 1950.

130. Trumbull, M. L., and Greiner, D. J.: Homologous Serum Jaundice: An Occupational Hazard to Medical Personnel, J. A. M. A. **145**:965-967 (March 31) 1951.

It seldom is possible to discover the source of the virus-bearing blood or how it infected the person who handled it. The disease in this respect may be regarded as occupational in origin, and victims are entitled to compensation. Rigid observance of asepsis is the best protection against infection.

Cat-Scratch Disease.—In regard to unusual or heretofore undescribed conditions, as in the case of "cat-scratch" disease, it occasionally happens that several observers in widely scattered places report a disease almost simultaneously. Foshay apparently noted the malady in connection with his studies on tularemia but did not publish his observations. French, Swiss, and subsequently two American groups of observers reported cases within the past year.[131] The disease is acquired by the scratch of a cat and is probably viral in origin. It resembles tularemia clinically but is milder and is unaffected by antibiotic therapy. Cats which convey the infection are not sick but transmit the pathogenic agent mechanically.

There still are a number of infectious diseases whose agents have not been isolated with certainty or are unknown. The common ones are "viral" pneumonia, "viral" dysentery, "viral" hepatitis, and infectious mononucleosis. There are several diseases of unknown causes in tropical countries called three-day fever, five-day fever, six-day fever, and so on. Some of these may be either dengue or pappatacci fever. Another grippe-like disease of similar nature lasting six days with characteristic symptoms or signs was studied in 250 patients in Central America.[132] The cause is unknown. Getting reported an outbreak of a measles-like infection in Massachusetts.[133] The diagnosis and cause have not been established. Reference is made elsewhere to an outbreak of an unusual disease in Louisiana, to a neurologic disease in Denmark, and to an encephalitis of unknown cause in North Dakota.

Manchurian or Epidemic Hemorrhagic Fever.—A disease recognized as Songo fever by the Japanese in Manchuria in 1939 affected a number of American troops in Korea in the late summer of 1951; 13% died.[133a] Its characteristics are chills, fever, photophobia, headache, cough, diarrhea, arthralgia, nausea, vomiting, and, after three or four days, small hemorrhages in the sclerae, kidneys, heart, pituitary, and elsewhere. Atypical lymphocytes appear resembling those of mononucleosis, and a leukemoid reaction may occur. A filtrable agent is suspected as the cause, and mites are thought to be the vector.

Epidemic Diarrhea.—The problem of epidemic diarrhea of newborn infants is unsolved. Another outbreak is reported in which no pathogens could be incriminated.[134] There were no deaths, and the attack rate was low. Boric acid solution

131. Debré, R., and others: Diseases Due to Cat's Scratches, Semaine hôp. Paris **26**:1895-1904 (May 30) 1950. Thélin, F., and Martin-du-Pan, R.: New Observations on Disease Due to Cat Scratches, Praxis **40**:74-76 (Jan. 25) 1951. Gsell, O.; Forster, R., and Klaus, E.: Virus-Scratch-Lymphadenitis (Disease Due to Cat Scratches, Lymphoreticulosis Benigna), Schweiz. med. Wchnschr. **81**:699-703 (July 21) 1951. Greer, W. E. R., and Keefer, C. S.: Cat-Scratch Fever: A Disease Entity, New England J. Med. **244**:545-548 (April 12) 1951. Daniels, W. B., and MacMurray, F. G.: Cat-Scratch Disease: Nonbacterial Regional Lymphadenitis, A. M. A. Arch. Int. Med. **88**:736-751 (Dec.) 1951.

132. Judson, W. E.: An Undescribed Idiopathic Fever on the Isthmus of Panama, Am. J. Trop. Med. **31**:275-283 (May) 1951.

133. Measles-like Infection, Incidence of Disease, Pub. Health Rep. **66**:1164 (Sept. 7) 1951.

133a. Manchurian Fever, Washington News, J. A. M. A. **147**:adv. p. 13 (Nov. 24) 1951.

134. Wegman, M. E.: An Epidemic of Diarrhea Among Breast-Fed Newborn Infants, J. A. M. A. **145**:962-965 (March 31) 1951.

used on the mother's nipples was suspected as a vector of infection, but staphylococci alone were cultivated from it. Neter studied a strain of Escherichia coli (D 433) isolated in England and supposedly a cause of infantile diarrhea.[135] The bacterium was found in the intestine of five patients and in the nasopharynx of two. The possibility of air-borne infection was raised. Whether strain D433 is a common cause of diarrhea is unknown, but feeding it to an infant caused diarrhea. Terramycin and aureomycin therapy caused clinical improvement but failed to do so in another epidemic apparently of viral origin.[47]

Wyatt and his group describe six cases of generalized cytomegalic inclusion disease in six infants.[136] Many other cases had been reported previously. There were nuclear and cytoplasmic inclusions in the salivary glands and other organs. They describe the first instance in which a virus was established as the cause of infantile enteritis. Infection occurs during intrauterine life and often is fatal.

Viral Dysentery.—Britten and others described outbreaks of "viral" dysentery, under the name epidemic diarrhea of unknown cause, in adults in three psychiatric hospitals.[137] The outbreaks occurred in December, 1946, and January, 1947, and lasted about three weeks. The attack rates ranged from 0 in some wards to 80% in others. The death rate was 0.57 to 4.7%, and was almost entirely confined to senile or otherwise debilitated patients. Clinically, the disease followed its usual mild form in the majority of cases. The rapidity of the spread of the disease and its localization in some wards, regardless of the same food and water supply to all, suggested close personal contact or air-borne infection as the means of spread. Similar epidemics affected a number of schools in 1947-1948.[138] Of interest are the first necropsy reports which have come to my attention. Six necropsies were performed. The intestinal contents were fluid and blood-stained. The mucosa was reddened, and the mesenteric vessels were congested. Microscopically there were stasis in capillaries and veins, thrombus formation, and hemorrhage and necrosis of the mucosa. Inflammatory exudate of slight degree, consisting of polymorphonuclear leucocytes, lymphocytes, and monocytes, extended into the submucosa. I observed another epidemic among nurses in October, 1951, similar to the one reported in medical students in 1944. Sigmoidoscopic observations and results of biopsy and cultural studies will be published.

Viral Pneumonias.—Interest in viral pneumonia has waned, as indicated by the few papers published on the subject. There has been no large epidemic since that of 1941 to 1943; yet, from time to time and in no relation to season, sporadic severe viral pneumonias are encountered. I reported on seven such cases in which differential diagnoses involved tuberculosis, typhoid, psittacosis-ornithosis, Q fever, infectious mononucleosis, and coccidioidomycosis, each of which may at any given

135. Neter, E., and Shumway, C. N.: E. Coli Serotype D433: Occurrence in Intestinal and Respiratory Tracts, Cultural Characteristics, Pathogenicity, Sensitivity to Antibiotics, Proc. Soc. Exper. Biol. & Med. **75**:504-507 (Nov.) 1950.

136. Wyatt, J. P.; Saxton, J.; Lee, R. S., and Pinkerton, H.: Generalized Cytomegalic Inclusion Disease, J. Pediat. **36**:271-294 (March) 1950.

137. Britten, S. A.; Rubenstein, A. D.; Raskin, N., and Strassmann, G.: Epidemic Diarrhea of Unknown Cause: Report of Outbreaks in 3 Massachusetts State Hospitals, New England J. Med. **244**:749-753 (May 17) 1951.

138. Ingalls, T. H., and Britten, S. A.: Epidemic Diarrhea in a School for Boys, J. A. M. A. **146**:710-712 (June 23) 1951.

time resemble another.[139] Diagnosis is important since different entities need specific treatment and epidemiologic management. Others report on 67 cases which exhibited a wide range of clinical variations and provided similar diagnostic difficulties.[140] King treated 10 patients with streptomycin and reported striking improvement in each.[141] No patients served as untreated controls.

Two patients with viral pneumonia were treated with corticotropin.[142] In one, the symptoms were relieved, but they recurred when the dose was diminished and were again relieved when the dose was increased. When corticotropin therapy was stopped, fever and symptoms recurred and were not controlled with aureomycin treatment. In the other, there were prompt defervescence and remission of symptoms, but fever returned during therapy, and the symptoms returned when therapy was stopped. Corticotropin may have had only an antipyretic action, but the rapid improvement of other symptoms suggests a more profound effect on the host. The infection itself apparently was not influenced. Herpes developed in one patient during therapy.

According to French physicians, the virus of influenza may cause disease identical with viral pneumonia.[143] Influenza virus A, as indicated by the chicken-cell-agglutination test, caused pneumonia in 69 of 237 patients. The blood of 140 patients did not contain agglutinins for chicken red cells or a cold agglutinin. In only 11 was cold agglutination found in high titer, but it vanished during the disease.

In a four-year period, Finland and Barnes found cold agglutination to occur in 75% of cases of viral pneumonia and not after bacterial pneumonias, influenza, tracheobronchitis, or other acute infection of the respiratory tract.[144] Viral pneumonia and cold agglutinin most frequently are found during the summer and autumn months. Since the titer of cold agglutinin usually develops in proportion to the gravity of the disease, it is likely to be low or absent in mild infections without pneumonia.

Frugoni and Magrassi, in an essay written in English, further advance their classification of the viral pneumonias into two large groups: (*a*) influenza-like disease with a short incubation period in which the primary attack is on the respiratory mucosa and (*b*) pneumonias with long incubation periods, such as Q fever, measles, or psittacosis, in which pulmonary involvement is one manifestation among

139. Reimann, H. A.: Severe, Sporadic Virus Pneumonias: Diagnostic and Therapeutic Problems, J. A. M. A. **144**:81-85 (Sept. 9) 1950.

140. Jordan, W. S.; Albright, R. W.; McCain, F. H., and Dingle, J. H.: Clinical Variations in Primary Atypical Pneumonia, Am. J. Med. **10**:3-20 (Jan.) 1951.

141. King, F. P.: Atypical Pneumonia Treated with Streptomycin: A Preliminary Report on the Effectiveness of Streptomycin in Atypical Pneumonia, Ann. Int. Med. **34**:141-147 (Jan.) 1951.

142. Kass, E. H.; Ingbar, S. H., and Finland, M.: Effects of Adrenocorticotrophic Hormone in Pneumonia: Clinical, Bacteriological and Serological Studies, Ann. Int. Med. **33**:1081-1098 (Nov.) 1950.

143. Cateigne, G.; Eyquem, A., and Hannoun, C.: Biologic Diagnostic Problems of Primary Atypical Pneumonia Due to a Virus, Presse méd. **58**:438-441, (April 22) 1950.

144. Finland, M., and Barnes, M. W.: Cold Agglutinin: VII. Tests for Cold Isohemagglutinins in Pneumonia and Other Respiratory Infections over a 4-Year Period, Am. J. M. Sc. **221**:152-157 (Feb.) 1951.

others of blood-disseminated disease.[145] To this extent their opinion coincides with my own in regard to separating the mild epidemic seasonal forms of viral pneumonia of short incubation period from the sporadic, nonseasonal severe cases which appear to be systemic diseases with pneumonia as a prominent feature. Their newly described "eosinophilmonocytic fever" is grouped with the systemic forms. They deprecate the term "primary atypical pneumonia" as strongly as I do. The pneumonias they write of are *typical* of new nosologic entities.

The inevitable confusion incident to undesirable names is evident in papers of several contributors.[146] Contrary to earlier recommendation, they use the inclusive term "primary atypical pneumonia" and group together the so-called viral pneumonia of unknown cause, rickettsial pneumonia, fungal pneumonias, and pneumonias of known viral origin on the basis of their clinical resemblance.[146] If, on this basis, an analogy were drawn with neurotropic viral diseases, one of them may be set up as "typical," and all the rest called atypical meningoencephalitis, regardless of their diversified causes. The absurdity of the plan is self-evident. The word "atypical" ought to be abandoned in naming entities. They are typical of themselves. The term nonbacterial pneumonia is less caliginous.[147]

The "grey lung" virus reported on by Andrewes in 1945 was found to be similar to several viruses: one isolated from cotton rats in 1944, one isolated by Rose in 1950, one isolated by Andrewes in 1951, and one presumably isolated from one of my patients. The details are described in a series of papers in the December, 1950, issue of *The British Journal of Experimental Pathology*. The viruses differ in a few respects and may be either unrelated ones or biologic variants of a single strain. The importance of these viruses is their possible relation to viral pneumonia, particularly since they are unusual ones and are susceptible to the effect of aureomycin and terramycin but not to that of chloramphenicol, penicillin, or streptomycin.

Geever and his associates describe 10 cases in which unusual pulmonary lesions were observed at necropsy in patients who had had other diseases and in whom pneumonia was unsuspected during life.[148] The lesions resembled those found in viral pneumonias. Progressive interstitial pulmonary fibrosis and adenomatosis may result from chronic disease.

Three patients with a peculiar form of fatal pneumonia were observed.[149] The disease lasted three to six months and was characterized by diffuse pneumonitis, fever, progressive dyspnea, and the presence of cytoid bodies in the retina. Histologic study revealed eosinophilia, hyaline membrane in the alveolar walls, hemorrhagic fluid in the alveoli, organization of the exudate, and extension of the metaplastic bronchiolar epithelium into adjacent areas. The cause is unknown, but the

145. Frugoni, C., and Magrassi, F.: Pneumonopathies Due to Virus and Rickettsiae in Relation to the So-Called "Primary Atypical Pneumonia," Sc. med. ital. **1**:203-218 (April-June) 1950.

146. Stuart-Harris, C. H.: Atypical Pneumonia, Brit. M. J. **2**:1457-1461 (Dec. 30) 1950. Bedson, S. P.: Primary Atypical Pneumonia, ibid. **2**:1461-1463 (Dec. 30) 1950.

147. Syverton, J.: Non-Bacterial Pneumonias, Dis. Chest. **18**:456-477 (Nov.) 1950.

148. Geever, E. F.; Neuberger, R. T., and Rutledge, E. K.: Atypical Pulmonary Inflammatory Reaction, Dis. Chest **19**:325-338 (March) 1951.

149. Tumulty, P. A.; Berthrong, M., and Harvey, A. M.: A Peculiar Pneumonia Associated with Retinal Cytoid Bodies, Bull. Johns Hopkins Hosp. **88**:239-263 (March) 1951.

general features resemble those of a viral infection. Four comprehensive reviews of the viral pneumonias are available.[150]

Psittacosis-Ornithosis.—An outbreak of ornithosis occurred among workers who handled turkey and chicken feathers.[151] Meyer and Eddie report a case in which Miyagawanella organisms were isolated repeatedly from the sputum of a man who had persistent productive cough for 10 years after an attack of psittacosis.[152] Complement-fixing antibodies in titers from 1:28 to 1:256 were demonstrated. Carriers evidently exist.

DISEASE CAUSED BY BACTERIA

Pneumonias.—The decline in the mortality rate of lobar pneumonia from 30 to less than 10% since sulfonamide compounds and antibiotic agents have been used led to a false impression that pneumonia has declined proportionately in incidence. Studies from widely scattered sources indicate pneumonia to be as prevalent as ever, but with proper therapy the duration and severity of the disease caused by pneumococci are less and the death rate is lower. In improperly or inadequately treated patients the disease is modified sufficiently to cause diagnostic confusion with forms of atypical pneumonia, and pneumococci, by which diagnosis otherwise could be made, often cannot be isolated or "typed."[153]

One group of investigators successfully treated patients with lobar pneumonia by giving an initial parenteral injection of penicillin and thereafter penicillin orally with "benemid" (*p*-[di-*n*-propylsulfamyl]-benzoic acid) to retard urinary excretion of penicillin.[154]

The results were as good as with parenteral therapy. In another study patients received aluminum penicillin orally alone with equally good results.[155] Patients with severe illness were treated parenterally.

Terramycin was successfully used in the treatment of 18 patients with pneumococcic pneumonia.[156] Improvement usually was evident within a few hours of the beginning of therapy, and the temperature fell to normal within 36 hours in every patient. The dose was initially 2 gm., followed by 1 gm. every six hours orally. The antibiotic caused gastrointestinal disturbances in 9 of the 25 patients. The

150. Reimann, H. A.: The Viral Pneumonias and Pneumonias of Probable Viral Origin, Medicine **26**:109-219 (May) 1947. Van Erp, T.: De primaire atypische pneumonieen van onbekende oorsprung, Leiden, E. J. Brill, 1947, pp. 1-124. Frugoni, C.; Magrassi, F., and Giunche, G.: Le malattie dell'apparato respiratorio da virus e da rickettsie, Rome, Luigi Pozzi, 1949. François, R.: Pneumonies à virus et pneumonie primitive atypique, Lyon, Emmanuel Vitte, 1950, pp. 1-190.

151. Irons, J. V.; Sullivan, T. D., and Rowen, J.: Outbreak of Psittacosis (Ornithosis) from Working with Turkeys or Chickens, Am. J. Pub. Health **41**:931-937 (Aug.) 1951.

152. Meyer, K. R., and Eddie, B.: Human Carrier of the Psittacosis Virus, J. Infect. Dis. **88**:109-125 (March-April) 1951.

153. Reimann, H. A.: The Changing Nature of Pneumonia, Ann. Int. Med. **33**:1246-1253 (Nov.) 1950.

154. Austrian, R., and others: The Efficacy of Modified Oral Penicillin Therapy of Pneumococcal Lobar Pneumonia, Bull. Johns Hopkins Hosp. **81**:264-269 (March) 1951.

155. Harvey, J. C., and Mirick, G. S.: The Treatment of Pneumococcal Lobar Pneumonia with Oral Aluminum Penicillin, Bull. Johns Hopkins Hosp. **81**:270-275 (March) 1951.

156. Melcher, G. W., Jr.; Gibson, C. D., Jr.; Rose, H. M., and Kneeland, Y., Jr.: Terramycin in the Treatment of Pneumococcic and Primary Atypical Pneumonia, J. A. M. A. **143**:1303-1308 (Aug. 12) 1950.

results obtained were as good as those brought about by penicillin or aureomycin therapy. Another group of patients was successfully treated with a single daily oral dose of 1 gm. of either aureomycin or chloramphenicol.[157]

Finland and his co-workers treated three patients having lobar pneumonia with corticotropin.[142] In each the symptoms disappeared rapidly after treatment was begun. In two pneumococci remained in the sputum during convalescence. In the third, fever and disease returned and the pneumonia spread when therapy was stopped. Aureomycin and penicillin were then given. Empyema developed. Curiously corticotropin, which so strikingly affects the sedimentation rate of erythrocytes in other diseases, failed to do so in pneumonia.

K. Pneumoniae Pneumonia.—Up to 1945 the mortality rate of pneumonia caused by K. pneumoniae (Friedländer's bacillus) was reported to be more than 50%, in contrast with the great reduction in mortality from other bacterial pneumonias. About one-sixth of patients recovered; one-third progressed to the chronic phase, and one-half died. Therapy with sulfonamide compounds, penicillin, and immune serum was ineffective. After the advent of streptomycin and its therapeutic use, many more patients recovered. Aureomycin treatment in one case gave strikingly good results.[158] Preliminary studies suggest that chloramphenicol may be of greater value. Lobectomy, pneumonectomy, and drainage of abscesses are recommended in the chronic stage, as reported in a study of 16 cases.[159]

Neva reviews the knowledge of pulmonary involvement during the typhoids and describes his own observations on 80 cases studied in Egypt.[160] In his experience, pneumonia never was primary. Abnormal pulmonary signs were present in 64% of patients with typhoid, but pneumonia in only nine, or 11%. Studies on 19 patients failed to reveal the pathogenic agent of the pneumonias. Apparently, pneumonia during typhoid usually is caused by other microbes. Evidence of bronchial irritation is common.

Meningitis.—Among 90 cases of meningitis caused by H. influenzae, treatment with streptomycin reduced the mortality rate to 3.4%.[161] In the majority of cases, improvement took place within six days after treatment was started. The results were as good in patients treated intramuscularly alone as in those who received streptomycin intrathecally. Sulfadiazine also was given, but its value was uncertain. Chloramphenical was used with success by others.[162]

Hoyne and Herzon reviewed the reported cases of meningitis caused by nonhemolytic streptococci.[163] There were 34 in which recovery occurred and 29 fatal

157. Kirby, W. M. M., and others: Comparision of Aureomycin and Chloramphenicol in the Treatment of Bacterial Pneumonia, J. A. M. A. **147**:110-114 (Sept. 8) 1951.

158. Nataro, M.; Shapiro, D., and Gordon, A. T.: Acute Primary Klebsiella Pneumonia, J. A. M. A. **144**:12-16 (Sept. 2) 1950.

159. Wylie, R. H., and Kirschner, P. A.: Friedländer's Pneumonia, Am. Rev. Tuberc. **61**:465-473 (April) 1950.

160. Neva, F. A.: Pulmonary Involvement in Typhoid and Paratyphoid Fevers, Ann. Int. Med. **33**:83-99 (July) 1950.

161. Appelbaum, E., and Nelson, J.: Streptomycin in the Treatment of Influenzal Meningitis: A Study of 90 Cases, with 96.6 per Cent Recovery, J. A. M. A. **143**:715-717 (June 24) 1950.

162. Prather, G. W., and Smith, M. H. D.: Chloramphenicol in the Treatment of Hemophilus Influenzae Meningitis, J. A. M. A. **143**:1405-1406 (Aug. 19) 1950.

163. Hoyne, A. L., and Herzon, H.: Streptococcic Viridans Meningitis: A Review of the Literature and Report of 9 Recoveries, Ann. Int. Med. **33**:879-902 (Oct.) 1950.

cases. Nonhemolytic or green-producing streptococci from time to time are blamed for causing different conditions, such as pneumonia and arthritis, but often there is a question whether they may be only secondary invaders in these diseases, as well as in meningitis. They are the unquestionable cause in only one disease—subacute bacterial endocarditis. Indifferent or green-producing streptococci may be confused with untypable pneumococci. Nevertheless, at times they may be pathogenic, and, if so, the disease they cause requires energetic therapy according to the sensitivity of the germ to any of the available antibiotic agents. In one instance, meningitis caused by enterococci followed spinal anesthesia.[164]

Meningitis occasionally is caused by infection with two varieties of bacteria. In one group of cases, H. influenzae was one of the organisms in nine patients.[165] The accompanying organisms, respectively, were Neisseria meningitidis (Neisseria intracellularis) in four cases, streptococci in three, and pneumococci in two. Meningitis in one patient was caused by pneumococci and colon bacilli. In Conn's patient a Pneumococcus and a strain of Klebsiella were present.[166] This knowledge emphasizes the importance of careful bacteriologic studies in each case and the selection of appropriate antibiotics either singly or in combination for the treatment of dual infections.

According to Nemir and Israel, therapy of pneumococcic meningitis in children with penicillin intramuscularly and sulfonamides orally has reduced the mortality rate from nearly 100% to about 19%.[167] Intrathecal therapy is not recommended except for the most desperately sick patients.

Subacute Bacterial Endocarditis.—Hunter regards the direct bactericidal effects of therapeutic agents, not merely their bacteriostatic action, to be of great importance in the treatment of subacute bacterial endocarditis.[60] Sensitivity tests of the causative organisms which measure growth inhibition only are misleading. In this respect, aureomycin, chloramphenicol, and probably terramycin may have less value than penicillin or streptomycin. Furthermore, a combination of penicillin and streptomycin causes rapid killing of nonhemolytic streptococci, but only during the phase of active growth. Studies are in progress to determine the effectiveness of 10 days of intensive therapy with combined antibiotics for subacute bacterial endocarditis.

According to Friedberg, the recovery rate in reports on controlled series of cases of subacute bacterial endocarditis is about 65%.[168] He believes the rate can be increased to more than 90%. The chief causes of failure are delay in beginning treatment because of error in diagnosis and inadequate therapy when bacteria are highly resistant. When bacteria are resistant, massive doses of penicillin, from 10,000,000 to 40,000,000 units daily, either alone or together with carinamide, or the use of dihydrostreptomycin or aureomycin substituted for or combined with

164. Keefer, C. S.: Bacterial Meningitis Following Lumbar Puncture and Spinal Anesthesia, Am. Pract. **1**:679-682 (July) 1950.

165. Vaden, E. B.; Rice, E. C., and Stadnichenko, V.: Meningitis Due to Simultaneous Double Infections in Children, J. A. M. A. **143**:1401-1404 (Aug. 19) 1950.

166. Conn, J. J., and Rosenow, O. F.: Mixed Meningitis: A Case of Combined Pneumococcus and Klebsiella Meningitis with Recovery, Arch. Int. Med. **85**:924-932 (June) 1950.

167. Nemir, R. L., and Israel, J.: Pneumococcic Meningitis in Infants and Children: Combined Therapy Using Penicillin and Sulfonamide, J. A. M. A. **147**:213-218 (Sept. 15) 1951.

168. Friedberg, C. K.: Subacute Bacterial Endocarditis: Revision of Diagnostic Criteria and Therapy, J. A. M. A. **144**:527-533 (Oct. 14) 1950.

penicillin, are recommended. Criteria for early diagnosis should be revised. Whenever a patient with an organic valvular lesion has unexplained fever for more than a week, treatment as for subacute bacterial endocarditis should be started while awaiting the results of blood culture and the measurement of sensitivity of the causative organism. If treatment be delayed until blood cultures are incubated or until embolic lesions or other structural injuries occur, the recovery rate is much less. If the disease subsides during therapy, it may be impossible to verify the diagnosis, but the risk of not treating endocarditis promptly justifies the procedure. Penicillin is the drug of choice and should be given for at least five weeks in doses of 1,200,000 units daily for the average case. If more than 0.08 unit of penicillin per cubic centimeter is needed to kill the bacteria in the test for sensitivity, the dosage should be doubled. If bacteremia persists, more penicillin should be given, up to 40,000,000 units, or penicillin should be given in combination with dihydrostreptomycin, 2 to 3 gm. daily, or aureomycin, 3 to 4 gm. daily, especially if bacteria other than streptococci are present. Curiously, the recovery rate was smaller in patients whose blood cultures were sterile than in those whose blood cultures showed growth.

Orgain and Donegan review experiences in the treatment of subacute bacterial endocarditis.[169] In their opinion, the most important factor in therapy is adequate dosage of penicillin, from 500,000 to 1,000,000 units a day. Various techniques of administration have no particular superiority, and added anticoagulant therapy is of no value. Treatment should last four to six weeks or longer if relapse occurs. The mortality rate in their series of 37 patients was 46%.

Resistant enterococci accounted for about 4% of Loewe's 157 cases of subacute bacterial endocarditis.[170] Robbins and Tompsett treated such patients with both penicillin and streptomycin,[171] as did Cates in England, who found resistant strains in 1% of cases.[172] Cates describes one patient in whom relapse was caused by the extraction of teeth while a protective "umbrella" of penicillin was used. One is appalled to read elsewhere that "wholesale removal of teeth" is advocated in the treatment of subacute bacterial endocarditis, in spite of no evidence to favor the procedure even if dental infection is suspected.[173] In two earlier publications, dental extraction actually was the cause of endocarditis in 25% of patients who had cardiovascular defects. The disease also occurred in 10% of 70 patients with valvular heart disease who underwent surgical procedures on the prostate gland.[174] If eradication of all "possible foci of infection" is to be accomplished, the entire respiratory, genitourinary, and gastrointestinal tracts would have to be extirpated.

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169. Orgain, E. S., and Donegan, C. K.: The Treatment of Bacterial Endocarditis, Ann. Int. Med. **33**:1099-1113 (June) 1951.

170. Loewe, L.; Candel, S., and Eiber, H. B.: Therapy of Subacute Enterococcus (Streptococcus Fecalis) Endocarditis, Ann. Int. Med. **34**:717-736 (March) 1951.

171. Robbins, W. C., and Tompsett, R.: Treatment of Enterococcal Endocarditis and Bacteremia: Results of Combined Therapy with Penicillin and Streptomycin, Am. J. Med. **10**:278-299 (March) 1951.

172. Cates, J. E.; Christie, R. V., and Garrod, L. P.: Penicillin-Resistant Subacute Bacterial Endocarditis Treated by a Combination of Penicillin and Streptomycin, Brit. M. J. **1**:653-656 (March 31) 1951.

173. Flippin, H. F.: Subacute Bacterial Endocarditis, Correspondence, J. A. M. A. **145**:1216 (April 14) 1951.

174. Merritt, W. A.: Bacterial Endocarditis as a Complication of Transurethral Prostatic Resection, J. Urol. **65**:100-107 (Jan.) 1951.

"Focal Infection."—The June, 1951, issue of *The Journal of the American Dental Association* contains an 80-page review of dental and medical views on the role of infection about the teeth in relation to general health and disease. The consensus is in agreement with my own conclusions published in 1940; namely, there is no good evidence to support the theory that a direct relationship exists between "infected teeth" and systemic disease or that removal of such teeth relieves or cures disease elsewhere in the body. Lederer expresses similar views anent tonsillectomy.[174a]

Streptococci.—Loosli's study of hemolytic streptococcic infections revealed how widespread infections may be caused by "skin dispersers."[175] Droplet air-borne and dust-borne infection can be controlled partially by oiling floors and bedding and with the use of aerosols, but uncontrolled infection by way of contact with the skin also occurs. Patients with hemolytic streptococcic infections should be isolated promptly, cared for by aseptic procedures, and receive penicillin to stop the spread of infection to others.

The question is raised whether all patients, especially children, with acute sore throat should be treated with penicillin regardless of the cause. At present, evidence of the value of penicillin used prophylactically against rheumatism would seem to favor the view that if bacteriologic diagnostic facilities are not available, every instance of exudative pharyngitis-tonsillitis should be regarded as streptococcic in origin and treated with penicillin. No doubt many instances of viral infection would then be included, and many persons unfortunately would be sensitized to penicillin.

In two studies reported from England, a sulfonamide compound called "sulphatriad" (a mixture of sulfathiazole, sulfamerazine, and sulfadiazine) when given to patients with tonsillitis or sore throat did not speed recovery, as compared with such patients who did not receive the drug.[176] While a clinical impression suggested some beneficial effect, it was not great enough to warrant the routine use of the drug. In half the cases the hemolytic Streptococcus was not the cause. In another controlled study of 475 cases of streptococcic tonsillitis and pharyngitis, aureomycin administration was more effective than penicillin therapy in shortening the course of disease slightly but was not as effective as penicillin treatment in eliminating streptococci from the throat.[177] Rheumatic fever developed in two penicillin-treated patients and in five controls. Therapy with penicillin depresses the formation of type-specific immune bodies in patients with hemolytic streptococcic pharyngitis.[177a] Failure to develop specific immunity increases the risk of subsequent infection.

174a. Lederer, F. L.: Indications for Tonsillectomy and Adenoidectomy, Postgrad. Med. **10**:191-196 (Sept.) 1951.

175. Loosli, C. G.; Smith, M. H. D.; Cline, J., and Nelson, L.: The Transmission of Hemolytic Streptococcal Infection in Infant Wards with Special Reference to "Skin Dispersers," J. Lab. & Clin. Med. **36**:342-359 (Sept.) 1950.

176. Macdonald, T. C., and Watson, I. H.: Sulphonamides and Acute Tonsillitis: A Controlled Experiment in a Royal Air Force Community, Brit. M. J. **1**:323-326 (Feb. 17) 1951. Landsman, J. B., and others: "Sore Throat" in General Practice, ibid. **1**:326-329 (Feb. 17) 1951.

177. Brink, W. R.; Rammelkamp, C. H.; Denny, F. W., and Wannamaker, L. W.: Effect of Penicillin and Aureomycin on the Natural Course of Streptococcal Tonsillitis and Pharyngitis, Am. J. Med. **10**:300-308 (March) 1951.

177a. Daikos, G., and Weinstein, L.: Streptococcal Bacteriostatic Antibody in Patients Treated with Penicillin, Proc. Soc. Exper. Biol. & Med. **78**:160-163 (Oct.) 1951.

Rheumatic Fever.—In studies on the prophylaxis of rheumatic fever, penicillin was given in amounts of 1,200,000 units in a 96-hour period to about 1,000 patients with tonsillitis or pharyngitis, and a similar number received no penicillin.[178] Ten of the treated persons acquired rheumatic fever later, as compared with 42 of the control persons. In some of these, an intervening infection caused by hemolytic streptococci of a different type occurred. Evidently, penicillin lessened the occurrence of rheumatic fever after infection with hemolytic streptococci.

In therapeutic tests on 11 patients with acute rheumatic carditis, 6 with initial involvement and 5 with recurrent attacks, corticotropin given over several days terminated the symptoms and signs of disease.[179] Four to 12 months later there was no sign of residual heart disease in patients who had had a single attack and no evidence of increased injury in those who had had recurrences.

According to Wolff, the mortality rate of rheumatic fever and heart disease in children is increasing in percentage, but only in relation to the decline of other fatal diseases of childhood.[180] Deaths from rheumatic fever have declined strikingly in the past decades.

Although one group of investigators succeeded in evoking subcutaneous nodules in rheumatic patients by the injection of blood, of solution of sodium chloride, and of hyaluronidase,[181] others failed to do so by injecting blood, trypsin, or fluid from the joint of a patient with rheumatoid arthritis.[182] Such contradictory results are just as difficult to explain as the success of some investigators in causing periarteritis nodosa experimentally and the failure of others who used essentially the same technique.

The specificity of the Aschoff nodule for rheumatic fever still is disputed. Granulomatous lesions were found in the myocardium in 13 of 63 patients who died from tuberculosis, and in seven they were said to be identical with Aschoff nodule. Apparently hypertensive or allergic reactions in a variety of conditions give rise to miliary granulomas.[183]

Brucellosis.—After various methods proposed for the treatment of brucellosis led to disappointment, Herrell and Barber reported better therapeutic results with a combination of antibiotic agents.[184] They give aureomycin hydrochloride orally in doses of 750 mg. every six hours, together with 1 gm. of dihydrostreptomycin injected intramuscularly twice daily, usually for 12 to 14 days. When focal lesions are present, aureomycin is given for 28 days with 0.5 gm. of streptomycin twice

178. Wannamaker, L. W., and others: Prophylaxis of Acute Rheumatic Fever by Treatment of the Preceding Streptococcal Infection with Various Amounts of Depot Penicillin, Am. J. Med. **10**:673-695 (June) 1951.

179. Wilson, M. G., and Helper, H. N.: Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in Acute Rheumatic Carditis, J. A. M. A. **145**:133-138 (Jan. 20) 1951.

180. Wolff, G.: Death Toll from Rheumatic Fever in Childhood, J. A. M. A **145**:719-724 (March 10) 1951.

181. Massell, B. F.; Coen, W. B., and Jones, T. D.: Observation Regarding Artificially Induced Subcutaneous Nodules in Rheumatic Fever Patients, Pediatrics **5**:909-123 (June) 1950.

182. Schwartz, S., and Steinbrocker, O.: Production of Rheumatic Subcutaneous Nodules, Am. Heart J. **40**:100-105 (July) 1950.

183. Valdes-Dapena, A., and Valdes-Dapena, M.: Rheumatic Nodules in Tuberculosis, J. A. M. A. **146**:1565-1569 (Aug. 28) 1951.

184. Herrell, W. E., and Barber, T. E.: A New Method for Treatment of Brucellosis, J. A. M. A. **144**:519-523 (Oct. 14) 1950.

daily. Treatment is best given to patients kept in bed, but they may be ambulatory. Thirty-five patients with infection caused by the abortus, melitensis, or suis varieties of Brucella were treated successfully when observed for 3 to 19 months. In discussion on this report, Eisele favors the addition of sulfadiazine to aureomycin and dihydrostreptomycin, but Herrell found this to be of no advantage. Knight reports rapid improvement in 13 patients after treatment with chloramphenicol, but there were recurrences in more than half of them.[185] Similar results are reported from the use of terramycin.[186] Aureomycin failed to prevent relapses with bacteremia in three cases of brucellosis caused by Br. suis.[187] The ideal form of therapy is yet to be found.

Because of the disagreement on whether an intradermal test for brucellosis evokes diagnostically confusing agglutinin in the blood, the problem was restudied by Carpenter and his co-workers.[188] Of 57 persons whose skin reacted to the injection of antigen intradermally, specific agglutinin in the serum appeared two weeks later in 17, or 30%. Agglutinin, previously absent, developed to titers ranging from 1:20 to 1:1280 and declined or disappeared one to three months later. No agglutinin appeared in 193 persons whose skin failed to react. Obviously it is only when the skin of sensitized persons reacts to intradermal injection of antigen that agglutinin for Brucella appears in a significant proportion of persons. Therefore, the diagnostic confusion is not great because the agglutinin response develops only in skin-sensitive subjects.

Two reports of cases describe brucellosis confined to the urinary tract.[189] The condition is akin to tuberculosis of the urinary tract and reminiscent of a case of typhoid pyelonephritis I described several years ago. The subject of meningoencephalitis caused by Brucella is reviewed by Nichols.[190] Two cases of probable "reinfection" brucellosis were observed.[191]

Spink studied the perplexing diagnostic problem of chronic brucellosis.[192] Many persons who have had brucellosis continue to complain of weakness, fatigue, aches, nervousness, and depression. Many of these are emotionally unstable persons. A diagnosis of chronic brucellosis can be made only if the patient has had the disease, if he has objective as well as subjective evidence of disease, if agglutinin is present in titer higher than 1 to 100, and, especially, if Brucella can be isolated from

185. Knight, V.; Ruiz-Sanchez, F., and McDermott, W.: Chloramphenicol in Treatment of Acute Manifestations of Brucellosis, Am. J. M. Sc. **219**:627-638 (June) 1950.

186. Killough, J. H.; Magill, G. B., and Smith, R. C.: Terramycin, Chloramphenicol and Aureomycin in Acute Brucellosis, J. A. M. A. **145**:553-558 (Feb. 29) 1951.

187. Green, T. W., and Stein, L.: Failure with Aureomycin in the Treatment of Infection with Brucella Suis, J. A. M. A. **144**:380-382 (Sept. 30) 1950.

188. Carpenter, C. M.; Deboer, C. J.; Klein, S. J., and Tempereau, C. E.: Agglutinin Response to Intradermal Tests for Sensitivity to the Brucella, J. Immunol. **65**:331-335 (Sept.) 1950.

189. Greene, L. F., and Albers, D. D.: Brucellosis of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **25**:638-640 (Nov. 8) 1950.

190. Nichols, E.: Meningo-Encephalitis Due to Brucellosis with the Report of a Case in Which B. Abortus Was Recovered from the Cerebrospinal Fluid, and a Review of the Literature, Ann. Int. Med. **35**:673-693 (Sept.) 1951.

191. Green, T. W.: Reinfection Brucellosis: A Report of 2 Cases, Ann. Int. Med. **35**:717-721 (Sept.) 1951.

192. Spink, W. W.: What is Chronic Brucellosis? Ann. Int. Med. **35**:358-374 (Aug.) 1951.

tissues or fluids. The intradermal test is not reliable. Disappointingly, therapy with antibiotics had no influence in reducing the number of patients who remained ill for a year as compared with the untreated ones.

Typhoid.—After his previous report, Smadel recommends the following regimen in treating typhoid: chloramphenicol in an initial oral dose of 3 to 4 gm., followed by 1.5 gm. orally every 12 hours during the febrile period, and by single daily 1.5-gm. doses for seven days until the 14th day of therapy.[193] This dosage reduces the danger of relapse, but hemorrhage and perforation still may occur because of injury done before therapy is started. Furthermore, therapy may mask the signs and symptoms of either of these serious occurrences.

Because patients with typhoid successfully treated with chloramphenicol showed little clinical improvement during the first three or four days of therapy, Smadel and his co-workers added cortisone to the regimen to hasten recovery.[194] Combined therapy in eight patients gave relief within 15 hours when large doses of cortisone and chloramphenicol were given; with smaller doses the average febrile period was 50 hours. According to Woodward, treatment with cortisone alone, which has no effect on Salmonella typhi, controlled the symptoms in six patients. Combined therapy or chloramphenicol given by itself is preferable. Evidently there is a drug-parasite relation peculiar to chloramphenicol and S. typhi. Aureomycin and streptomycin also inhibit S. typhi in artificial media, yet chloramphenicol alone is able to reach and affect typhoid bacilli in the body and influence the disease.[195]

Salmonella.—Felsen emphasizes the importance of inapparent infections with Salmonella in outbreaks of disease in institutions.[198] Persons who carry Salmonella organisms may or may not be sick. The clinical picture is not characteristic, but sigmoidoscopy reveals diffuse, perinodular hyperemia of the mucosa, with hypertrophy and hyperplasia or focal necrosis of the solitary lymph nodules. The changes resemble those caused by Shigella. They may be present in persons with asymptomatic or subclinical disease. The diagnosis is confirmed by isolating the bacilli from the material obtained from the mucosal crypts. Persons who carry Salmonella, particularly those who handle food, are common sources of infection. Three factors have been responsible for intramural outbreaks in institutions: lack of centralized control, delay in dealing with an epidemic, and secrecy or concealment. Felsen recommends initial and routine monthly fecal cultures on all food handlers in hospitals, all nurses in pediatric services, and all obstetric patients. The procedure is laborious and is apt not to be performed generally. An epidemiologist should be on the staff of every large hospital. The discovery of Salmonella in 3% of nearly 3,000 hen's eggs indicates another potential hazard of infection from uncooked

193. Smadel, J. E.; Bailey, C. A., and Lewthwaite, R.: Synthetic Fermentation Type Chloramphenicol (Chloromycetin) in Typhoid Fever: Prevention of Relapses by Adequate Treatment, Ann. Int. Med. **33**:1-17 (July) 1950.

194. Smadel and others.[84] Woodward, T. E., and others: Treatment of Typhoid Fever: II. Control of Clinical Manifestations with Cortisone, Ann. Int. Med. **34**:10-19 (Jan.) 1951.

195. Werner, C. A.; Knight, V., and McDermott, W.: Comparison of the Antityphoid Activities of Aureomycin and Chloramphenicol on Bacteria Artificially Localized in Vivo, abstracted, J. Clin. Invest. **30**:682 (June) 1951.

196. Footnote deleted.

197. Footnote deleted.

198. Felsen, J.; Weil, A. J., and Wolarsky, W.: Inapparent Salmonella Infections in Hospitals, J. A. M. A. **143**:1135-1138 (July 29) 1950.

eggs.[199] The classification of the more than 150 strains of Salmonella organisms continues to be a problem. They may be placed into five major groups: (*a*) paratyphi A; (*b*) paratyphi B, typhimurium, and Types Derby, Bredeny, and San Diego; (*c*) choleraesuis and Types Oranienburg, Montevideo, Bareilly, Newport, Thompson, and Tennessee; (*d*) typhi, enteritidis, and Types Panama, Dublin, and Napoli, and (*e*) anatis and Types Senftenberg, Give, Meleagris, and Newington. New ones undoubtedly will be added.

Bacillary Dysentery.—Although sulfadiazine is of value in the treatment of Shigella enteritis or bacillary dysentery, it has limitations. Sulfonamide-resistant strains of bacilli occur; patients may be hypersensitive to the drugs, and the toxic effects of the drugs may be greater in dehydrated patients. Three antibiotics are therapeutically effective, streptomycin, polymyxin B, and chloramphenicol. Chloramphenicol given orally in doses of 250 mg. every four hours for 6 to 11 days for an average total dose of 11.5 gm. gave good results in 34 of 35 treated patients.[200]

In a study on patients with ulcerative colitis, sulfonamide compounds given orally reduced the number of bacteria in the feces and altered the type of bacteria present for as long as six weeks.[201] After this time the flora reverted to its former state despite medication. Streptomycin and aureomycin given orally had a similar effect, but it lasted only a week or so. Chloramphenicol had little effect and penicillin none at all.

Tularemia.—Although an attack of tularemia is believed generally to confer permanent immunity to subsequent infection, instances of reinfection or recurrence are reported.[202] Tularemia at times is a serious disease of sheep in the western states. It is transmitted by ticks and can be controlled by disinfection.[203] Agglutinin for Pasteurella tularensis persists five to seven months. A water supply contaminated with Past. tularensis caused illness in four persons in Montana.[204]

Plague.—Bubonic plague in a hunter who cleaned cottontail rabbits in New Mexico led to field studies in which wild rodents in the vicinity, including rabbits, are implicated as natural sources of the disease. Five cases of plague, two of them fatal, were observed in New Mexico by Link.[205] In an endemic area, plague should be suspected if the axillary, inguinal, or other lymph nodes are swollen during an acute febrile disease. Penicillin is of no value in treatment.

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199. Carter, M. J.; Powell, M. P., and Borts, O. H.: Salmonella in Hen Eggs, Pub. Health Rep. **65**:778-781 (June 16) 1950.

200. Ross, S., and others: Chloramphenicol (Chloromycetin) Therapy in Shigella Enteritis, J. A. M. A. **143**:1459-1460 (Aug. 26) 1950.

201. Marshall, H. C.; Palmer, W. L., and Kirsner, J. B.: Effects of Chemotherapeutic Agents on Fecal Bacteria in Patients with Chronic Ulcerative Colitis, J. A. M. A. **144**:900-903 (Nov. 11) 1950.

202. Green, F. W., and Eigelsbach, H. T.: Immunity in Tularemia: Report of 2 Cases of Proved Reinfection, Arch. Int. Med. **85**:777-782 (May) 1950.

203. Jellison, W. L., and Kohls, G. M.: Persistence of Agglutinins Against Pasteurella Tularensis in Serums of Naturally Infected Sheep, J. Am. Vet. M. A. **117**:405-408 (Nov.) 1950.

204. Jellison, W. L.; Epler, D. C.; Kuhns, E., and Kohls, G. M.: Tularemia in Man from a Domestic Rural Water Supply, Pub. Health Rep. **65**:1219-1226 (Sept. 22) 1950.

205. Link, V. B.: Plague Epizootic in Cottontail Rabbits, Pub. Health Rep. **65**:696 (May 26) 1950; Plague, J. A. M. A. **144**:375-377 (Sept. 30) 1950.

According to Meyer, streptomycin in doses of 4 gm. daily is the therapeutic agent of choice for plague.[206] The dosage may be reduced on the third or fourth day, and, for reasons of economy, streptomycin may be replaced by sulfadiazine after the fifth day. In severe disease or for pneumonic plague, administration of aureomycin or terramycin (2 to 4 gm.) and antiplague serum globulin is recommended. If antibiotics are unavailable, sulfadiazine alone may be used. An epidemic of plague developed in India despite prophylactic inoculations of persons in a community.[207]

Tuberculosis.—The discovery of streptomycin, or other antituberculotic agents, and of cortisone and the controversy over the value of BCG vaccine have caused a resurgence of interest in tuberculosis. A symposium of eight relevant papers appeared in the November, 1950, issue of *The American Journal of Medicine.* For several years, interest in the treatment of tuberculosis with streptomycin was dominant. It seemed relatively simple to decide on its use until several new chemicals were found also to affect the tubercle bacilli. The problem now to settle is which of the new therapeutic agents is best and should they be used separately, consecutively, or in combination. At present all of them are to be regarded as adjuvants to established methods of management.

A Swedish committee reports beneficial effects in 94 patients with pulmonary tuberculosis after treatment with *p*-aminosalicylic acid (PAS) over a period of three months in daily dosage of 10 gm.[208] More rapid improvement occurred than in untreated control patients. Others report beneficial effects in 12 of 22 patients; the conditions of 8 were not improved, and in 2 the disease progressed.[209] Tubercle bacilli were demonstrable persistently in the sputum of 13 patients. *p*-Aminosalicylic acid therapy was not as effective as streptomycin treatment. The best results followed the use of the drugs combined.[210] British physicians report similar observations.[211] Amithiozone, a thiosemicarbazone related to sulfathiazole discovered by Domagk, was used in the treatment of more than 10,000 patients in Europe with reported encouraging results.[28] Its use in combination with streptomycin and *p*-aminosalicylic acid may have superior value. The subject is presented in a symposium in the January, 1950, number of *The American Review of Tuberculosis.* Amithiozone is a relatively toxic drug. As discussed elsewhere in this review, the therapeutic importance of the drug is not limited to tuberculosis. Terramycin is bacteriostatic for Myco. tuberculosis but less active than strepto-

206. Meyer, K. F.: Modern Therapy of Plague, J. A. M. A. **144**:982-985 (Nov. 18) 1950.

207. Ghosh, P. K.: Outbreak of Plague in Epidemic Form Treated with Streptomycin and Sulfadiazine, Indian M. Gaz. **85**:441-444 (Oct.) 1950.

208. Therapeutic Trials Committee of the Swedish National Association Against Tuberculosis: Para-Aminosalicylic Acid Treatment in Pulmonary Tuberculosis: Comparison Between 94 Treated and 82 Untreated Cases, Am. Rev. Tuberc. **61**:597-612 (May) 1950.

209. Dooneief, A. S.; Buchberg, A., and Steinbach, M. M.: Para-Aminosalicylic Acid (PAS) in Chronic Pulmonary Tuberculosis, New England J. Med. **242**:859-862 (June 1) 1950.

210. Potter, B. P.: A Clinical Appraisal of the Value of Para-Aminosalicylic Acid With and Without Streptomycin in the Treatment of Tuberculosis, Dis. Chest **17**:509-523 (May) 1950.

211. Marshall, G., and others: Treatment of Pulmonary Tuberculosis with Streptomycin and Para-Amino-Salicylic Acid: A Medical Research Council Investigation, Brit. M. J. **2**:1073-1085 (Nov. 11) 1950.

mycin.[212] French observers report streptomycin-dependent tubercle bacilli as the cause in several cases of tuberculosis in which the disease became worse after streptomycin administration.[213]

Smith and his co-workers made an extensive study to determine the value of many surface-active agents as disinfectants against tubercle bacilli.[214] The results were disappointing. Of 142 agents tested, only 1 had sufficient activity to be worthy of further study. A number of other compounds were tested also, but the list is too long for discussion here.

The mortality rate among 93 patients with tuberculous meningitis treated in England was about 50% after a year of treatment with streptomycin.[215] The authors point out how uncertain recovery is. The disease is associated with an elaborate tissue response with which antibiotics are unable to deal unaided. Intrathecal injection of streptomycin was thought to aid in the lysis of exudate.

Since Brainerd and Eagle also point out the value of intrathecal injection of streptomycin in addition to parenteral injection, tuberculous meningitis may prove to be the exception among the meningitides in which this route of therapy is desirable.[216] In their experience only 6 of 27 patients were alive 18 to 31 months after the beginning of treatment. Most patients who were aided received more than 60 mg. per kilogram of body weight per day. At the beginning of the third month of treatment no further improvement occurred in about one-half of the surviving patients, probably because of the development of resistance of the bacilli to streptomycin. It was hoped that streptokinase would dissolve fibrin and prevent blockage of the cerebrospinal circulation. Unfortunately, in one series of cases[217] no benefit was obtained. The agent itself caused unpleasant side-effects.

Cortisone and Corticotropin in Tuberculosis.—While the clinical symptoms of tuberculosis may be favorably influenced for a time by administration of cortisone, the hormone is known to inhibit the formation of granulation tissue, to interfere with the activity of macrophages, and to deplete the lymphocytic resources of the body, factors which are believed to be necessary for the natural recovery from tuberculosis. To test the effect of cortisone therapy in this respect, guinea pigs experimentally infected with tuberculosis were treated with cortisone and streptomycin separately and cortisone combined with streptomycin.[218] At the end of the experiment, animals treated with cortisone had more extensive tuberculous

212. Hobby, G. L.; Lenert, T. F.; Donikian, M., and Pikula, D.: The Tuberculostatic Activity of Terramycin, Am. Rev. Tuberc. **63**:434-440 (April) 1951.

213. Dufourt, A.; Brun, J.; Viallier, J., and Kalb, J. C.: Bacteriologic Dependence on Streptomycin and Clinical Exacerbation Due to Streptomycin, J. méd. Lyon **32**:351-356 (April 20) 1951.

214. Smith, C. R., and others: The Bactericidal Effect of Surface-Active Agents on Tubercle Bacilli, Pub. Health Rep. **65**:1588-1600 (Dec. 1) 1950.

215. Cairns, H.; Smith, H. V., and Vollum, R. L.: Tuberculous Meningitis, J. A. M. A. **144**:92-96 (Sept. 9) 1950.

216. Brainerd, H. D., and Eagle, H. R.: The Effect of Streptomycin on Tuberculous Meningitis, Ann. Int. Med. **33**:397-410 (Aug.) 1950.

217. Lorber, J.: Streptokinase as an Adjunct in the Treatment of Tuberculous Meningitis, Lancet **1**:1334-1337 (June 23) 1951.

218. Spain, D. M., and Molomut, N.: Effects of Cortisone on the Development of Tuberculous Lesions in Guinea Pigs and on the Modification by Streptomycin Therapy, Am. Rev. Tuberc. **62**:337-344 (Oct.) 1950.

lesions than the others. Similar results were noted in rats.[219] Cortisone seemed to lower the natural resistance to experimental infection. Cortisone given to patients with other diseases apparently favors the exacerbation of latent tuberculosis. In the Sept. 15, 1951, issue of *The Journal of the American Medical Association,* three papers contain descriptions of patients with arthritis treated with corticotropin or cortisone in whom tuberculosis developed, and another appeared elsewhere.[220] In each patient, severe tuberculosis appeared to be activated by hormone therapy. One of my patients with disseminated lupus erythematosus, treated elsewhere with cortisone, died of tuberculosis.

According to Lurie's group, cortisone administration profoundly altered the pathogenesis of tuberculosis in rabbits.[221] The results are confusing and difficult to reconcile with those of others. Cortisone treatment increased the number of tubercle bacilli in the lungs of susceptible animals but retarded the dissemination of the disease to a degree comparable with that which occurs in naturally resistant animals. Apparently cortisone treatment increases the phagocytic activity of the reticuloendothelial cells, and more bacilli are retained than in the controls. Despite the greater numbers of bacilli in the lungs of the cortisone-treated rabbits, their dissemination to the regional lymph nodes was much less than in untreated ones. Cortisone, therefore, transforms a rabbit of high susceptibility to tuberculosis into one that reacts more like a naturally resistant rabbit. When tuberculin was injected into the lungs of rabbits previously sensitized with tubercle bacilli, a severe pneumonic reaction occurred, but, if animals were treated with corticotropin, the reaction was much less severe. When corticotropin therapy was withdrawn, a fresh pneumonic reaction appeared within three days. Evidently corticotropin suppresses the violence of the reaction.[222] Cortisone canceled the protective action of vaccination in mice infected with virulent tubercle bacilli and increased the susceptibility of mice to bacilli of low invasiveness.[223]

LeMaistre and his colleagues treated seven patients with far-advanced tuberculosis in whom lesions could be seen in the larynx.[224] Corticotropin and cortisone therapy caused abrupt improvement subjectively and objectively. In each, however, the effect was temporary and could not be prolonged by continued therapy. The reactivity of host tissue to the hormone is unrelated to the reactivity of the skin to the Mantoux test. The sudden improvement in patients' conditions may occur

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219. Michael, M.; Cummings, M. M., and Bloom, W. L.: Course of Experimental Tuberculosis in the Albino Rat as Influenced by Cortisone, Proc. Soc. Exper. Biol. & Med. **75**:613-616 (Nov.) 1950.

220. Kleinschmidt, R. F., and Johnston, J. M.: Miliary Tuberculosis in a Cortisone Treated Patient: Case Report with Autopsy, Ann. Int. Med. **35**:694-702 (Sept.) 1951.

221. Lurie, M. B.; Zappasodi, P.; Dannenberg, A. M., and Swartz, I. B.: Constitutional Factors in Resistance to Infection: The Effect of Cortisone on the Pathogenesis of Tuberculosis, Science **113**:234-237 (March 2) 1951.

222. Smith, D. T., and Reinmuth, O. M.: Effect of ACTH on Pneumonia Induced with Tuberculin in Lungs of Sensitized Rabbits, Federation Proc. **10**:419 (March) 1951.

223. Solotorovsky, M.; Gregory, F. J., and Stoerck, H. C.: Loss of Protection by Vaccination Following Cortisone Treatment in Mice with Experimentally Induced Tuberculosis, Proc. Soc. Exper. Biol. & Med. **76**:286-288 (Feb.) 1951.

224. LeMaistre, C., and others: Effects of Adrenocorticotropic Hormone and Cortisone in Patients with Tuberculosis, J. Clin. Invest. **30**:445-456 (May) 1951.

after treatment with streptomycin, which acts on the bacteria, or with hormones, which act on the host. At present there does not appear to be any evidence favoring the use of cortisone for the treatment of tuberculosis.

Further application of Middlebrook and Dubos' hemagglutination reaction reveals its value in the diagnosis of tuberculosis.[225] The test gave a positive reaction in 92% of serum samples from patients with tuberculosis and a negative reaction in almost all of 216 serums from nontuberculous persons or patients. In Smith and Scott's experience the test is not useful in determining clinical activity.[226] It gave a positive result in the majority of patients whose disease had been arrested. The test gave a positive result after several volunteers had had a reaction to an injection of tuberculin, but especially after vaccination with BCG.

BCG Vaccine.—Controversy over the matter of artificial immunization against tuberculosis persists and will continue until better methods for its evaluation become available. Scandinavian investigators are enthusiastic about the results of vaccination. Hertzberg, for example, found 83% of vaccinated persons to retain allergy for nine years, and among 13,000 of them no deaths from tuberculosis occurred.[227] According to Swedish army physicians the incidence of both primary and reinfection tuberculosis was reduced significantly. Rosenthal of this country, in studies on infants vaccinated within three months of birth, reported twice as many cases of tuberculosis in the unvaccinated infants used for control.[228] Up to June, 1950, more than 10,000,000 persons throughout the world were vaccinated. The work is being conducted by the International Tuberculosis Campaign.[229]

Many American authorities are skeptical of the value of BCG vaccine. In the United States the death rate from tuberculosis was already below 30 per 100,000 in 1950, and if the present rate of decline continues it will be 15 per 100,000 in 1960.[230] Neither BCG vaccine nor streptomycin contributed to this remarkable improvement. According to Anderson and Palmer, controversy about the indications for and value of BCG vaccination has not been resolved by research and extensive clinical application in recent years.[231] Questions asked 25 years ago still are not answered. There is wide variation of opinion in regard to the number of bacilli necessary to give rise to a relatively durable immunity and to the duration and degree of allergy produced. There is no proof that vaccination alone was responsible for the decline in the incidence of and mortality from tuberculosis in several European countries. In Iceland, for example, the mortality rate fell from 200 to 34 per 100,000 over two decades without the use of BCG vaccine. With these figures in mind, the currently accepted measures for the control of tubercu-

225. Rothbard, S.; Dooneief, A. S., and Hite, K. E.: Practical Application of a Hemagglutination Reaction in Tuberculosis, Proc. Soc. Exper. Biol. & Med. **74**:72-75 (May) 1950.

226. Smith, D. T., and Scott, N. B.: Clinical Interpretation of Middlebrook-Dubos Hemagglutination Test, Am. Rev. Tuberc. **62**:121-127 (Aug.) 1950.

227. Hertzberg, G.: Factors Influencing the Effectiveness of BCG Vaccination, Acta tuberc. scandinav. **23**:338-350, 1949.

228. Rosenthal, D. R.: Immunologic Aspects of BCG Vaccination in Strictly Controlled Study in Infants from Tuberculous Households, J. Pediat. **36**:399-420 (April) 1950.

229. BCG Vaccination on a World-Wide Scale, Pub. Health Rep. **66**:1158-1162 (Sept. 7) 1951.

230. Current Outlook for Tuberculosis, Statist. Bull. Metrop. Life Insur. Co. **31**:1-4 (Nov.) 1950.

231. Anderson, R. J., and Palmer, C. E.: BCG, J. A. M. A. **143**:1048-1051 (July 22) 1950.

losis should be used wherever feasible. If used at all, BCG vaccine should be given to persons most likely to contract tuberculosis and its effects studied accurately and controlled. In Dickey's opinion, the beneficial results from the use of BCG vaccine can be surpassed by the use of the usual accepted measures for prevention.[232]

Myers, who always has protested the use of BCG vaccine, reviews the history of its development.[233] If infection with Myco. tuberculosis itself does not result in dependable immunity, what, he justly asks, can be expected from vaccination? The chief problem lies in the unsettled dispute whether hypersensitivity after infection or vaccination is harmful or beneficial. Allergy to tuberculoprotein is regarded by some as undesirable and to be avoided. No adequately controlled study of BCG vaccination ever was conducted over a period long enough to judge its value. The claims thus far published in favor of BCG vaccination apply to only 3% of cases of tuberculosis in Myers' view, and nothing is known of its effects on the other 97%. His own successful endeavor in controlling tuberculosis in Minnesota would have been hampered had BCG vaccine been used. In rare instances, BCG vaccine causes a tuberculous abscess at the site of injection and swelling of the axillary lymph nodes.[234] In the face of the uncertain value of BCG vaccination in tuberculosis, French investigators have extended its use to leprosy because the skin reaction to lepromin becomes positive after vaccination.[235]

In testing 10,000 persons with purified protein derivative of tuberculin in small and large amounts, peculiarities in distribution of reactors were encountered.[236] Reactions to injection of 0.0001 mg. occurred in 5 to 30% and were roughly in accordance with the expected geographic variation in the prevalence of tuberculosis. Reactions to 0.005 mg., however, showed a peculiar geographic concentration east of New Mexico and south of Kansas, especially in Louisiana and Mississippi, where about 72% responded to the stronger dose and only 9% to the weaker. This suggests the existence of some widespread factor in this area, perhaps a pathogenic micro-organism allergenically related to Myco. tuberculosis, which causes an infection as yet unrecognized. A similar unexplained difference in reaction to tuberculin was observed in northern India in natives living at different altitudes.[236a]

Sarcoidosis.—In respect to the peculiar geographic localization of certain reactors to tuberculin as discussed in the preceding paragraph, epidemiologic observations on sarcoidosis are of interest. In a study of 226 cases of sarcoidosis in Army personnel, by far the greatest number of patients came from the arc of states along the seaboard from Virginia to Texas, and most of them from rural areas.[237] The

232. Dickey, L. B.: The BCG Controversy, Dis. Chest **18**:502-507 (Nov.) 1950.

233. Myers, J. A.: Immunity in Tuberculosis, J. A. M. A. **146**:1492-1500 (Aug. 18) 1951.

234. Beyer, W.: Is Vaccination with BCG Entirely Harmless? München. med. Wchnschr. **93**:171-172 (June 26) 1951.

235. Immunobiologic Effect of BCG in Leprosy, Foreign Letters, J. A. M. A. **143**:1512 (Aug. 26) 1950.

236. Palmer, C. E.; Ferebee, S. H., and Peterson, O. S.: Studies of Pulmonary Findings and Antigen Sensitivity Among Student Nurses, Pub. Health Rep. **65**:1111-1131 (Sept. 1) 1950.

236a. Bates, L. E.; Busk, T., and Palmer, C. E.: Research Contribution of BCG Vaccination Programs: II. Tuberculin Sensitivity at Different Altitudes of Residence, Pub. Health Rep. **66**:1427-1441 (Nov. 2) 1951.

237. Michael, M., Jr.; Cole, R. M.; Beeson, P. B., and Olson, B. J.: Sarcoidosis: Preliminary Report on a Study of 350 Cases with Special Reference to Epidemiology, Am. Rev. Tuberc. **62**:403-407 (Oct.) 1950.

distribution suggests several possibilities: (*a*) the concentration of an unknown etiologic agent in this region, akin to the regional distribution elsewhere of the agents of coccidioidomycosis, histoplasmosis, and perhaps rickettsialpox; (*b*) the unusual response to a common infectious agent by persons influenced by the environment in the southeast; (*c*) the possibility that the high proportion of negative reactors to tuberculin is a factor of epidemiology rather than an actual feature of the disease, and (*d*) the possibility that the reported higher incidence of sarcoidosis in Negroes is only apparent and is related to the higher proportion of Negroes in the southeast.

In another study, 20 patients with sarcoidosis received BCG vaccination.[238] They were unable to develop or maintain skin sensitivity to tuberculin. Such anergy to tuberculin does not establish sarcoidosis as a peculiar form of tuberculosis but appears to be caused by nonspecific interference with the immune mechanism. In Bjørnstad's experience, 50, or 70%, of 71 patients with sarcoidosis failed to react to 10-mg. doses of tuberculin injected intracutaneously.[239] Roentgenograms of the chest showed lesions probably caused by previous tuberculosis in 11 of the 50. A negative reaction to 1 mg. of tuberculin, therefore, is an aid in differentiating the two diseases.

Pinkerton informed me of two cases diagnosed as sarcoidosis in which, after search, Histoplasma organisms were found in the adrenal glands. European investigators report the isolation of a mumps-like virus from 7 of 10 patients with sarcoidosis.[240] Perhaps it actually was mumps virus and had no connection with sarcoidosis.

Leprosy.—Johansen and Erickson discuss the current status of therapy of leprosy.[241] A group of sulfone compounds is said to be the most satisfactory drugs ever used. Streptomycin, aureomycin, and amithiozone also are effective in therapy, but the value of *p*-aminobenzoic acid and lupulon (beta-lupulic acid) is undetermined. "Sevinon" (undecylenic acid for oral administration) and antihistaminic agents have no antileprotic properties.

Leprosy recurred in six patients in whom it appeared to be arrested by treatment with sulfones two to three years before.[242] Relapses probably can be lessened if therapy is continued for some time after the disease is arrested.

The hemagglutination test for tuberculosis devised by Middlebrook and Dubos is useful in the study of leprosy.[243] The titer in active cases of leprosy was higher than in arrested ones and often was much higher than in cases of tuberculosis.

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238. Israel, H. L.; Jones, M.; Stein, S. C., and Aronson, J. D.: BCG Vaccination in Sarcoidosis, Am. Rev. Tuberc. **62**:408-417 (Oct.) 1950.

239. Bjørnstad, R. T.: Tuberculin Sensitivity in Boeck's Sarcoid, Acta tuberc. scandinav. **24**:15-37, 1950.

240. Löfgren, S., and Lundbäck, H.: Isolation of Virus in Several Cases of Boeck's Sarcoid, Wien. klin. Wchnschr. **63**:398-400 (June 1) 1951.

241. Johansen, F. A., and Erickson, P. T.: Current Studies of Therapy in Leprosy, J. A. M. A. **144**:985-989 (Nov. 18) 1950.

242. Erickson, P. T.: Relapse Following Apparent Arrest of Leprosy by Sulfone Therapy, Pub. Health Rep. **65**:1147-1157 (Sept. 8) 1950.

243. Levine, M.: Hemagglutination of Tuberculin Sensitized Sheep Cells in Hansen's Disease (Leprosy), Proc. Soc. Exper. Biol. & Med. **76**:171-173 (Jan.) 1951.

Only three cases have been reported in which Clostridium botulinum was present in wounds. No evidence of its pathogenicity was noted until a fatal case was observed in which symptoms of botulism occurred after a compound fracture. Cl. botulinum Type A was present in the wound.[244]

DISEASES CAUSED BY FUNGI

Histoplasmosis.—The gap is closing between the comparatively few recognized fatal cases of histoplasmosis and the apparently great number of persons in whom past infection is indicated only by calcified areas in the lungs and the reaction of the skin to histoplasmin. Instances of acute disease were observed in which recovery ensued.[245]

According to Tucker, there is a discrepancy in the fact that, although 38% of tested persons in Panama reacted positively to the histoplasmin skin test, no case of histoplasmosis has been recognized there since Darling's report of cases in 1906.[246] Two possibilities to account for the puzzle are (*a*) a cross reaction to other antigenically related fungi, and (*b*) the fact that nonfatal cases have been unrecognized. The incidence of persons reacting to the test rose sharply after the second decade of life. Only two reacted to coccidioidin; 60% to tuberculin. In Norway 53 of 1,074 persons tested with histoplasmin reacted positively, yet in none was there any sign of disease of the lungs.[247] Fifty also reacted to tuberculin. Probably other fungal infections in Norway have antigenic relationship with Histoplasma capsulatum.

In experimental studies three of five normal dogs contracted the disease after exposure for two to five months to dogs with histoplasmosis.[248] The disease did not occur in 25 persons who had household contacts with infected dogs. Nevertheless, dogs must be considered as a potential source of disease because Histoplasma organisms are disseminated in their saliva, sputum, vomitus, feces, and urine. The fungus was isolated repeatedly from soil in an unused silo in Indiana. Three men who had handled the soil acquired histoplasmosis.[249]

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244. Davis, J. B.; Mattman, L. H., and Wiley, M.: Clostridium Botulinum in a Fatal Wound Infection, J. A. M. A. **146**:646-648 (June 16) 1951.

245. Wheeler, W. E.; Friedman, V., and Saslow, S.: Simultaneous Nonfatal Systemic Histoplasmosis in Two Cousins, Am. J. Dis. Child. **79**:806-819 (May) 1950. Klingberg, W. G.: Generalized Histoplasmosis in Infants and Children: Review of Ten Cases, One with Apparent Recovery, J. Pediat. **36**:728-741 (June) 1950. Furcolow, M. L.: Further Observations on Histoplasmosis: Mycology and Bacteriology, Pub. Health Rep. **65**:965-994 (Aug. 4) 1950. Miller, I. R., and Grossman, S.: Benign Histoplasmosis in Siblings, J. A. M. A. **147**:753-755 (Oct. 20) 1951.

246. Tucker, H. A.: Histoplasmin, Tuberculin and Coccidioidin Sensitivity on the Isthmus of Panama: Preliminary Report of 500 Patients, Am. J. Trop. Med. **30**:865-870 (Nov.) 1950.

247. Böe, J.; Linden, V., and Tveit, J.: Histoplasmin and Coccidioidin Sensitivity in Norway, Acta med. scandinav. **139**:196-202 (March 17) 1951.

248. Prior, J. A., and Cole, C. R.: Studies on the Communicability of Histoplasmosis, Am. Rev. Tuberc. **63**:538-546 (May) 1951.

249. Grayston, J. T.; Loosli, C. G., and Alexander, E. R.: The Isolation of Histoplasma Capsulatum from Soil in an Unused Silo, Science **114**:323-324 (Sept. 28) 1951.

The house cat and the opossum have been added to the list of animals from which H. capsulatum has been isolated.[250]

Haplomycosis, a disease of animals, is caused by a fungus which resembles H. capsulatum. The disease was found as a natural infection of squirrels, mice, and rats in Arizona.[251] Elsewhere other animals are affected. Probably, as in the case of histoplasmosis, man at times may be infected.

Raftery studied the case of a 7-year-old child who had what seemed to be an acute attack of appendicitis.[252] An "injected" appendix was removed. Histologic study revealed histiocytes laden with yeast cells which on culture were H. capsulatum. The observation led to a review of 436 appendixes previously removed. Among these, bodies resembling H. capsulatum were found in 54. Many of the patients had had evidence of chronic disease with recurrent attacks of abdominal pain and nausea. In eight, roentgenograms of the chest showed enlarged lymph nodes or diffuse infiltration of the lungs. It is unlikely, however, that all 54 patients had histoplasmosis. It is not possible with certainty to identify H. capsulatum on morphologic grounds in tissue specimens. Yet the study further indicates that histoplasmosis clinically apparent or inapparent often occurs and at times may account for some of the dubious diagnoses of "chronic" appendicitis.

Further attempt to discover a therapeutic agent was made. In mice infected with H. capsulatum, treatment with quinacrine hydrochloride (atabrine® dihydrochloride) evidently was suppressive.[253] About twice as many untreated mice survived as compared with controls. In patients, therapy with ethyl vanillate, despite its toxicity, seemed to be helpful.[254]

In 1949 I reported on two patients suspected of having sarcoid disease in whom histoplasmosis was discovered.[255] Dr. Henry Pinkerton informed me of similar experience. Histoplasmosis may have been engrafted on patients with sarcoidosis; the two diseases may have been coincidental, or histoplasmosis may, at times, give rise to sarcoidosis or disease indistinguishable from it. Further intriguing data have accumulated. In Loosli's study, as in previous ones, the highest prevalence ratio of persons sensitive to the histoplasmin skin test occurs in the lower Mississippi basin, an area which to some extent overlaps the area of greatest incidence of sarcoidosis as discovered in military personnel.[256] Whether there is any connection in this respect between histoplasmosis and sarcoidosis cannot at present be said.

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250. Emmons, C. W.: Histoplasmosis: Animal Reservoirs and Other Sources in Nature of the Pathogenic Fungus, Histoplasma, Am. J. Pub. Health **40**:436-440 (April) 1950.

251. Jellison, W. L.: Haplomycosis in Montana Rabbits, Rodents, and Carnivores, Pub. Health Rep. **33**:1057-1063 (Aug. 18) 1950.

252. Raftery, A.: Subclinical Histoplasmosis: Gastrointestinal Histoplasmosis of Children, J. A. M. A. **145**:216-219 (Jan. 27) 1951.

253. Campbell, C. C., and Saslow, S.: Atabrine Therapy of Histoplasma Infection in Mice, Pub. Health Rep. **66**:570-577 (May 4) 1951.

254. Christie, A., and others: Treatment of Disseminated Histoplasmosis with Ethyl Vanillate, Pediatrics **7**:7-18 (Jan.) 1951.

255. Reimann, H. A., and Price, A. H.: Histoplasmosis Resembling Sarcoidosis, Tr. A. Am. Physicians **57**:112-115, 1949.

256. Loosli, C. G.; Beadenkopf, W. G.; Rice, F. A., and Savage, L. J.: Epidemiological Aspects of Histoplasmin, Tuberculin and Coccidioidin Sensitivity, Am. J. Hyg. **53**:33-57 (Jan.) 1951.

Many features of histoplasmosis and coccidioidomycosis are similar, but they differ in these respects: Erythema nodosum and lesions of bones occur less often in histoplasmosis, and gastrointestinal ulcers have not been reported in coccidioidomycosis.[257]

Coccidioidomycosis.—An outbreak of coccidioidomycosis was observed in a California forestry camp.[258] Over a period of four months, seven patients were admitted to a hospital, where one died from meningitis during the disseminated form of the disease. Roentgenographic evidence of pulmonary involvement was present in six. Headache, cough, pain in the chest, sore throat, anemia, malaise, fever, eosinophilia, and lymphadenopathy were the commonest symptoms and signs. Since other boys among the 61 in the group had had similar but mild symptoms at the same time, an epidemiologic study was made. A skin reaction to coccidioidin was demonstrated in 20, and the complement-fixation test gave a positive reaction in 10. The skin test, when first made, gave a negative reaction in two of the seven patients in the hospital. The histoplasmin skin test reaction was positive in about 8% of the group and in the same percentage of a control group, so that there was little reason to suppose that cross sensitization occurred. Coccidioidal meningitis may last nearly four years.[259] The diagnosis, which was not made until near death, could have been made in an early stage from clinical and laboratory data had the disease been in mind.

Looney and Stein reemphasize the dangers of handling cultures of the fungus.[260] They report eight cases in which infection was contracted in a laboratory. One was fatal, and another patient was sick 14 months with involvement of bones. Twenty-five other members of laboratory personnel reacted positively to coccidioidin, indicating that they had had subclinical infection.

According to Brueck and Buddingh, numerous pathogenic fungi grow well in the yolk sac of the chick embryo.[261] The application of this knowledge will facilitate experimental studies. Conant outlines appropriate methods for the diagnosis and recognition of diseases caused by fungi which often mimic tuberculosis.[262] For a thorough critique of much of the nonsense which has been perpetrated concerning the treatment of fungal diseases of the skin, reference to Mitchell's paper is advised.[263]

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257. Beadenkopf, W. G., and Loosli, C. G.: Histoplasmosis, Tuberculosis and Coccidioidomycosis, J. A. M. A. **146**:621-624 (June 16) 1951.

258. Kritzer, M. D.; Biddle, M., and Kersel, J. F.: An Outbreak of Primary Pulmonary Coccidioidomycosis in Los Angeles County, California, Ann. Int. Med. **33**:960-990 (Oct.) 1950.

259. Rosen, E., and Belber, J. P.: Coccidioidal Meningitis of Long Duration: Report of a Case of 4 Years and 8 Months' Duration, with Necropsy Findings, Ann. Int. Med. **34**:796-809 (March) 1951.

260. Looney, J. M., and Stein, T.: Coccidioidomycosis: Hazard Involved in Diagnostic Procedures, with Report of a Case, New England J. Med. **242**:77-82 (Jan. 19) 1950.

261. Brueck, J. W., and Buddingh, G. J.: Propagation of Pathogenic Fungi in the Yolk Sac of Embryonated Eggs, Proc. Soc. Exper. Biol. & Med. **76**:258-261 (Feb.) 1951.

262. Conant, N. F.: Laboratory Diagnosis of Pulmonary Mycoses, Am. Rev. Tuberc. **61**:690-704 (May) 1950.

263. Mitchell, J. H.: Ringworm of Hands and Feet, J. A. M. A. **145**:541-546 (June 9) 1951.

RICKETTSIAL AND OTHER DISEASES

Q Fever.—Association with infected livestock is a major factor in the spread of Q fever to man in California.[264] The control of the disease, therefore, depends on the eradication of the infection in cattle, sheep, and goats.[265] An unsuccessful attempt was made to rid cows of natural infection to prevent its transmission to man. In the dosage used, aureomycin given intravenously or by intramammary infusion failed to eliminate Coxiella burnetii from the milk.[266] Dust-borne Coxiella organisms may cause disease. They were recovered from the dust-laden air of a dairy and of a sheep ranch.[267] Milk, food, or water are unlikely transmitters of infection.

German observers report an epidemic of Q fever in a hospital, involving patients, physicians, and other personnel.[268] It was traced to a carrier, a laboratory worker, who had been exposed to the disease and had had chronic Q fever pneumonia of five months' duration. Infection apparently was spread to others by air-borne droplets or by indirect methods. Thirty-eight persons were infected in the hospital and seven in the laboratory. Unusual examples of Q fever were observed; one was a case of grave, prolonged encephalitis. Aureomycin was therapeutically effective. According to Gsell, in Switzerland, Q fever appears in three clinical forms, namely pneumonic, systemic, and meningoencephalitic.[269] Therapy with aureomycin was successful. Aureomycin seemed to have beneficial effect on Q fever in this country, but some patients obtained no relief.[270]

Typhus.—An attack of typhus does not confer lifelong immunity. About one-fourth of a population of a Russian village had typhus 10 to 20 years after a previous attack.[271] One wonders if the diagnosis of the supposed early attacks can be relied on.

The use of the Craigie-type vaccine as tested during an epidemic of typhus at Belsen, Germany, did not prevent the disease or diminish its incidence.[272] Vacci-

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264. Huebner, R. J., and Bell, J. A.: Q Fever Studies in Southern California: Summary of Current Results and a Discussion of Possible Control Measures, J. A. M. A. **145**:301-305 (Feb. 3) 1951.

265. Lennette, E. H., and Clark, W. H.: Observations on the Epidemiology of Q Fever in Northern California, J. A. M. A. **145**:306-309 (Feb. 3) 1951.

266. Luoto, L.; Huebner, R. J., and Stoenner, H. G.: Q Fever Studies in Southern California: XII. Aureomycin Treatment of Dairy Cattle Naturally Infected with Coxiella Burnetii, Pub. Health Rep. **66**:199-204 (Feb. 16) 1951.

267. De Lay, P. D.; Lennette, E. H., and De Ome, K. B.: Q Fever in California: II. Recovery of Coxiella Burnetii from Naturally-Infected Air-Borne Dust, J. Immunol. **65**:211-220 (Aug.) 1950.

268. Siegert, R.; Simrock, W., and Ströder, U.: Epidemic Outbreak of a Fever in a Hospital, Ztschr. Tropenmed. u. Parasitol. **2**:1-40 (July) 1950.

269. Gsell, O.: Clinical Aspects of Q Fever, Helvet. med. acta **17**:279-300 (Oct.) 1950.

270. Clark, W. H.; Lennette, E. H., and Meiklejohn, G.: Q Fever in California: III. Aureomycin in the Therapy of Q Fever, A. M. A. Arch. Int. Med. **87**:204-217 (Feb.) 1951.

271. von Borman, F.: Does Typhus Produce Life-Long Immunity? Deutsche med. Wchnschr. **75**:826-827 (June 16) 1950.

272. Davis, W. A.: Typhus at Belsen: II. Clinical Course of Epidemic Typhus in Persons Who Had Received Craigie Typhus Vaccine, Ann. Int. Med. **34**:448-465 (Feb.) 1951.

nation appeared to shorten the course of typhus and lessen its severity when applied in two or more doses from one to three months before infection.

The occurrence of so unusual a condition as Rocky Mountain spotted fever on Long Island, New York, is apt to give an impression that the disease has spread or at least was recently introduced there. However, in a historical study, Miller found records of cases in 1908 and 1912.[273] It appears also that the dog tick, a carrier of the disease, existed on Long Island as early as 1875. It is possible that Rocky Mountain spotted fever always has been endemic on Long Island, as it is wherever rodents, dogs, and ticks abound.

Two cases of Rocky Mountain spotted fever were observed for the first time in Panama.[274] The first proved outbreak of jungle yellow fever also was reported from Panama and from Costa Rica, where wild monkeys also are infected.[275]

Two cases of rickettsialpox were observed in residents of Boston.[276] It would be unusual if that disease were limited to New York City and its environs, from which all cases thus far have been reported. More cases probably will be discovered elsewhere.

Leptospirosis.—In an editorial, Sacks discusses the problem of leptospirosis.[277] There appear to be about seven pathogenic strains of Leptospira, namely, icterohemorrhagiae, grippotyphosa, sejroe, canicola, hebdomadis, bataviae, and pomona. They are widely distributed in the world, but only L. icterohemorrhagiae causes Weil's disease. The rest are said to cause less severe illness. Confusion has arisen in nomenclature from the giving of different names to one strain. For example, L. pomona and bovine leptospiras of American origin called the New Jersey and New York strains are indistinguishable antigenically.[278] The subject of canicola fever was reviewed.[279]

L. bataviae, first recognized in Indonesia, was recovered from patients during an outbreak of 78 cases of leptospirosis in Puerto Rico.[280] Leptospiremia was demonstrated in more than half of the patients. Penicillin, streptomycin, aureomycin, chloramphenicol, terramycin, and combinations of aureomycin and strepto-

273. Miller, J. K.: Rocky Mountain Spotted Fever on Long Island, Ann. Int. Med. **33**:1398-1406 (Dec.) 1950.

274. Rodaniche, E., and Rodaniche, A.: Spotted Fever in Panama: Isolation of the Etiologic Agent from a Fatal Case, Am. J. Trop. Med. **30**:511-517 (July) 1950.

275. Courtney, K. O.: Report on the Recent Outbreak of Jungle Yellow Fever in Panama, Am. J. Pub. Health **40**:417-426 (April) 1950.

276. Franklin, J.; Wasserman, E., and Fuller, H. S.: Rickettsialpox in Boston: Report of a Case, New England J. Med. **244**:509-511 (April 5) 1951. Pike, G.; Cohen, S., and Murray, E. S.: Rickettsialpox: Report of Serologically Proved Case Occurring in a Resident of Boston, ibid. **243**:913-915 (Dec. 7) 1950.

277. Sacks, M. S.: The Problem of Leptospirosis, editorial, Ann. Int. Med. **33**:481-486 (Aug.) 1950.

278. Gochenour, W. S.; Yager, R. H., and Wetmore, P. W.: Antigenic Sensitivity of Bovine Strains of Leptospirae (United States) and Leptospira Pomona, Proc. Soc. Exper. Biol. & Med. **74**:199-202 (May) 1950.

279. Rosenberg, B. L.: Canicola Fever: Review, with Report of 2 New Cases, Am. J. Med. **11**:75-91 (July) 1951.

280. Gochenour, W. S., and others: Indonesian Weil's Disease in Puerto Rico and the United States, Federation Proc. **10**:408-409 (March) 1951.

mycin and cortisone and aureomycin had no particular beneficial effect in the treatment. According to Hall and others, it is doubtful whether these antibiotics are worthy of further trial in this disease.[281]

An outbreak caused by L. pomona, ordinarily found in swine, also was reported for the first time in this country.[282] In circumstances similar to those I described several years ago, 50 of 80 persons who bathed in a creek in Alabama became sick after 2 to 10 days. None had jaundice, and all recovered. L. pomona was not isolated, but specific agglutinin was found in the serums of 18 of 22 patients, and of some hogs, cows, horses, and mules, but not in the serum of rats in the vicinity.

Diagnostic problems arose in the Puerto Rico outbreak because of the symptomatic diversity of the disease and its inadequate description in textbooks. Similar problems were faced by Gsell in Switzerland.[283]

Kala-Azar.—An accidental infection with Leishmania donovani occurred in a laboratory worker whose only signs or symptoms of disease were local; that is, no systemic disease was evident.[284] The authors believe it to be the first autochthonous case in the United States and the first instance of laboratory infection. They apparently are unaware of the case of a Chinese bacteriologist who accidentally aspirated a culture from a pipette and acquired kala-azar. Other patients also have exhibited the disease in the United States but had been infected in the Orient.

Endemic malaria in this country, including Puerto Rico, seems to have reached the vanishing point.[285] Spraying houses with DDT (dichloro-diphenyl-trichloroethane) has kept them free of mosquitoes. There is no evidence of the development of DDT-resistant mosquitoes. In 1950, 2,214 cases were reported, as compared with 62,763 cases reported in 1945.[286] In checking 676 supposed cases as reported, parasites were demonstrable in only 26. Evidently many diagnoses are erroneous. Temporary increases in the number of cases may be expected after the return of military personnel from endemic regions.

Diagnosis of malaria and of diseases caused by microfilaria can be made easily by demonstrating the microbes in a thin smear of "dermal juice" obtained by scarification of the skin of the scapular region.[287]

Mass treatment with hetrazan® (1-diethylcarbamyl-4-methylpiperazine dihydrogen citrate) of the population of the island of St. Croix, Virgin Islands, after a year showed a 79% reduction of "microfilaria-positive" persons as compared with

281. Hall, H. E., and others: Evaluation of Antibiotic Therapy in Human Leptospirosis, Ann. Int. Med. **35**:981-998 (Nov.) 1951.

282. Schaeffer, M.: Leptospiral Meningitis: Investigation of a Water-Borne Epidemic Due to L. Pomona, abstracted, J. Clin. Invest. **30**:670-671 (June) 1951.

283. Gsell, O.: Leptospiroses as Special Form of Infection, with Contribution to Aureomycin Therapy, Wien. Ztschr. inn. Med. **31**:81-94 (March) 1950.

284. Terry, R. L.; Lewis, J. L., and Sessoms, S. M.: Laboratory Infection with Leishmania Donovani: A Case Report, Am. J. Trop. Med. **30**:643-649 (Sept.) 1950.

285. Andrews, J. M.: Malaria Reduced to the Vanishing Point, abstracted, Pub. Health Rep. **65**:1689 (Dec. 15) 1950.

286. Malaria Approaching Extinction in United States, Government Services, J. A. M. A. **146**:1245 (July 28) 1951.

287. Van den Berghe, L., and Chardome, M.: An Easier and More Accurate Diagnosis of Malaria and Filariasis Through the Use of the Skin Scarification Smear, Am. J. Trop. Med. **31**:411-413 (July) 1951.

untreated persons.[288] The drug evidently is of value in eliminating a large proportion of carriers.

Toxoplasmosis is receiving attention in Europe. In Germany, serologic evidence of infection was demonstrated in 49 of 122 dogs.[289] Two to five per cent of dogs presumably are infected. Hares were found to be infected in Denmark.[290] Apparently, the danger of transmission to human beings, as in tularemia, must be considered. Treatment with both diasone® (sulfoxone sodium) and promin® (glucosulfone sodium) controlled infections with Toxoplasma in mice.[291]

MISCELLANEOUS

Poultry more frequently are sources of human disease than is generally realized. Twenty-six diseases may be listed in this respect, including representatives of viral, bacterial, fungal, protozoal, and metazoal cause.[292] Brucellosis, salmonellosis, equine encephalomyelitis, "swine erysipelas," and Newcastle disease may be mentioned. There are more than 80 known diseases which may be transmitted from animals to man.[293] They are known as zoonoses.

In three papers published in the July, 1951, issue of the *American Journal of Public Health and The Nation's Health,* the matter of infections accidentally acquired in laboratories is discussed. Reports of 1,342 infections and 39 deaths were gathered, but many more unreported cases no doubt occur. Bacteria were implicated in 775 cases, viruses in 265, rickettsiae in 200, fungi in 63, and parasites in 39. The diseases oftenest contracted were brucellosis, tuberculosis, tularemia, typhoid, streptococcosis, psittacosis, Q fever, and coccidioidomycosis.

Various aspects of biologic warfare were discussed by three authors and in an anonymous pamphlet.[294] All agree that the danger so far as man is concerned directly has been exaggerated, that it is almost impossible to cause widespread epidemics, and that no new terrorizing microbic agents have been discovered. Small epidemics of various diseases may, of course, be started in a number of ways. Awareness of the possibility of such attacks is important, and diagnostic facilities should be available immediately for their detection.

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288. Hewitt, R. I., and others: The First Year's Results of a Mass Treatment Program with Hetrazan for the Control of Bancroftian Filariasis on St. Croix, American Virgin Islands, Am. J. Trop. Med. **30**:443-452 (May) 1950.

289. Otten, E.; Westphal, A., and Kajahn, E.: Epidemiology of Toxoplasmosis: Dogs as a Source of Infection of Human Toxoplasmosis, Klin. Wchnschr. **29**:343-345 (May 15) 1951.

290. Christiansen, M., and Siim, J. C.: Toxoplasmosis in Hares in Denmark: Serologic Identity of Human and Hare Strains of Toxoplasma, Lancet **1**:1201-1202 (June 2) 1951.

291. Cross, J. B.: Diasone and Promin as Therapeutic Agents in Experimental Toxoplasmosis, Proc. Soc. Exper. Biol. & Med. **76**:548-551 (March) 1951.

292. Brandly, C. A.: Poultry Diseases as Public Health Problems, Pub. Health Rep. **66**:668-672 (May 25) 1951.

293. Diseases Transmitted to Man by Animals, Chron. World Health Organ. **5**:132-135 (May) 1951.

294. Haas, V. H.: Medical Aspects of Civil Defense in Biologic Warfare, J. A. M. A. **145**:900-905 (March 24) 1951. What You Should Know About Biological Warfare, Publication PA-2, United States Federal Civil Defense Administration, February, 1951. Langmuir, A. D.: The Potentialities of Biological Warfare Against Man: An Epidemiological Appraisal, Pub. Health Rep. **66**:387-399 (March 30) 1951. Redewill, F. H.: Biologic Warfare, abstracted, Official Program of the Scientific Assembly of the 100th Annual Session of the American Medical Association, Atlantic City, June 11-15, 1951, p. 99.

From a survey of medical problems among Eskimos, one is surprised to learn that epidemics of poliomyelitis, meningococcic meningitis, typhoid, whooping cough, and measles are not uncommon.[295] Tularemia, botulism, brucellosis, and rabies occur. Although polar regions contain the fewest persons per square mile, epidemics are favored by crowding into small huts to conserve heat in the winter and by lack of sanitation in the short warm season.

A year or two ago attention was called to the prevalence of trichinosis among animals and men in the Arctic regions. Now, report is made of the frequency of hydatid disease in dogs, foxes, moose, caribou, rodents, and other animals in Alaska.[296] Except for noting considerable "clinical evidence of echinococcosis" in man and that skin tests with Echinococcus antigen gave reactions in 20 to 30% of several groups of persons, no information on human disease was given. Hydatid disease rarely is suspected in patients unless they come from southeastern Europe or other known endemic areas. However, indigenous cases have occurred in Maryland, Louisiana, Mississippi, Missouri, Indiana, New York, and recently in California.[297] The long-predicted increase in the incidence of the disease in this country has not occurred, despite the large number of sheep raised.

Nutritional Deficiency.—In questioning previous views concerning the supposed adverse effect of nutritional deficiency on resistance to infection in animals, Balch tested a number of patients nutritionally depleted by disease.[298] There was no difference in response in cachectic patients with hypoproteinemia as compared with healthy control subjects in regard to reaction to an injection of diphtheria toxoid in persons who were "Schick-negative." The response was even better in certain patients than in the controls. Antibody production continues up to the time of the death in some. No relation between response to antibody and the development of infection was noted. Rats starved for 36 hours had twice as many phagocytosing leucocytes, which had engulfed three times as many bacteria, as well-fed ones.[299] On the other hand, according to Payne, the matter of protein depletion, together with other factors, may play a role in constitutional resistance to tuberculosis.[300]

Alarm raised by the fear of infection during leucopenia often leads to intensive prophylactic treatment. Kerby and Martin, however, show that severe leucopenia did not interfere with the removal of bacteria from the blood of intact rabbits or

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295. Haldeman, J. C.: The Problem of Alaskan Eskimos, Pub. Health Rep. **66**:912-917 (July 20) 1951.

296. Rausch, R., and Schiller, E. L.: Hydatid Disease (Echinococcosis) in Alaska and the Importance of Rodent Intermediate Hosts, Science **113**:57-58 (Jan. 19) 1951.

297. Tucker, H. A.: Hydatid Disease at the Los Angeles County Hospital, 1936-1948, with a Report of First Autochthonous Case from California, Am. J. Trop. Med. **31**:83-89 (Jan.) 1951.

298. Balch, H. H.: Relation of Nutritional Deficiency in Man to Antibody Production, J. Immunol. **64**:397-410 (May) 1950.

299. Kuna, A.; Blattberg, B., and Reiman, J.: Effect of Starvation on Phagocytosis in Vivo, Proc. Soc. Exper. Biol. & Med. **77**:510-514 (July) 1951.

300. Payne, H. M.: Body Mechanisms in Progressive Tuberculosis, Pub. Health Rep. **66**:1263-1272 (Oct. 5) 1951.

ones poisoned with hemotoxic drugs.[301] Phagocytic leucocytes seem to exert their important function at the local source of bacteremia, not on circulating bacteria.

Further evidence is presented that plasma cells, not the lymphocytes, are the cellular sources of antibodies. According to Reiss and his associates, there was no direct evidence for either theory, until bacteria against which animals were sensitized were seen to agglutinate on the surface of certain lymphoid cells of antibody-forming lymph nodes.[302] The cells belonged to the plasma-cell series.

Harrell and Aikawa found alterations in the permeability of membranes and capillary walls to be affected similarly by infections and by allergic factors.[303] They suggest possible therapeutic procedures to control the movement of fluids through the membranes. It must be borne in mind, however, that certain changes induced by infection, including fever, may represent a natural mechanism for defense, and interference with them may not be beneficial.

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301. Kerby, G. P., and Martin, S. P.: Splanchnic Removal of Bacteria from the Blood Stream of Leukopenic Rabbits, J. Exper. Med. **93**:189-196 (Feb.) 1951.

302. Reiss, E.; Mertens, E., and Ehrich, W. E.: Agglutination of Bacteria by Lymphoid Cells in Vitro, Proc. Soc. Exper. Biol. & Med. **74**:732-735 (Aug.) 1950.

303. Harrell, G. T., and Aikawa, J. K.: Alteration in the Permeability of Membranes During Infections, J. A. M. A. **147**:232-238 (Sept. 15) 1951.

News and Comment

GENERAL NEWS

Deaths from Heart Disease and Cancer.—The Federal Security Agency has announced that deaths from heart disease and cancer among children of school age exceed in number deaths from all infections and parasitic diseases combined. Dr. Leonard A. Scheele, Surgeon General of the United States Public Health Service, emphasized that there has been an over-all decline in the number of all deaths from diseases in childhood, including those due to both heart disease and cancer, but that the decline in the infectious and parasitic diseases has been overwhelmingly greater. The death rate from infectious and parasitic diseases in the group 5 to 19 years of age dropped from 48.2 per 100,000 in 1933 to 11.5 per 100,000 in 1948. During the same period heart and cancer deaths in the group dropped from 19.8 to 13.0 per 100,000 persons. Accidents continue as the leading cause for all deaths in the age group, totaling 11,348 in 1948, a rate of 3.28 per 100,000 children.

ANNOUNCEMENTS

Distribution of Yellow Fever Vaccine.—The Surgeon General of the Public Health Service has made the following announcement concerning the distribution of yellow fever vaccine. In the United States, the Rocky Mountain Laboratory of the Public Health Service is the only laboratory on the World Health Organization's list of institutions producing approved yellow fever vaccine. Because the vaccine is highly thermolabile and must be stored and transported at a subfreezing temperature, strict control of its handling is required. The policy for distribution of the vaccine is outlined below:

1. The Director of the Rocky Mountain Laboratory, Hamilton, Mont., in collaboration with the Laboratory of Biologics Control, National Institutes of Health, is responsible for setting standards for the transportation, storage, and administration of the yellow fever vaccine. Shipments of the vaccine are to originate from the Rocky Mountain Laboratory and be routed directly to the user, except as provided in 3 below. The vaccine is not to be redistributed.

2. The vaccine will be distributed in the United States to Public Health Service facilities; Department of Defense installations; organizations with large numbers of employees going into yellow fever areas; one health department of a state in which a yellow fever clinic of the Public Health Service is not available. The Epidemiology and Immunization Branch of the Division of Foreign Quarantine is responsible for approving facilities for the receipt of the vaccine and will conduct necessary investigations to insure compliance with requirements for handling the vaccine.

3. The vaccine may be sold to private concerns, or their agents, to be sent abroad for inoculation of employees in yellow fever areas. It may also be sold to approved foreign governments. Inasmuch as the vaccine is on the restricted commodity list of the Office of International Trade, Department of Commerce, all sales for the purpose of exportation must be approved by that agency. Orders not meeting the requirements of the Office of International Trade will be referred to the Administrative Officer of the Microbiological Institute.

National Science Board Elections.—Chester I. Barnard, president of the Rockefeller Foundation, was elected chairman of the National Science Board of the National Science Foundation at its second annual meeting held in Washington, D. C., Dec. 3, 1951. Mr. Barnard succeeds James B. Conant, president of Harvard University, who was the first chairman of the Board, elected to serve the initial term which began Dec. 12, 1950. Edwin B. Fred, president of the University of Wisconsin, was reelected vice-chairman of the National Science Board. The new chairman and vice-chairman were elected for two-year terms of office as prescribed by the National Science Foundation Act of 1950.

Four members of the Executive Committee whose terms had expired were also reelected. These were Mr. Barnard; Detlev Bronk, president of the Johns Hopkins University and president of the National Academy of Sciences; Lee A. DuBridge, president of the California Institute of Technology, and Elvin C. Stakman, chief of the Division of Plant Pathology and Botany at the University of Minnesota.

The Executive Committee consists of nine members to be chosen by the National Science Board, and the Director of the National Science Foundation, member ex officio. The other five members of the Executive Committee are Dr. Conant; Paul M. Gross, vice-president of Duke University; Robert F. Loeb, director of medical services, Presbyterian Hospital, New York; J. C. Morris, vice-president, Tulane University, and Alan T. Waterman, director of the Foundation. The smaller group is authorized to act for the 24-member National Science Board in such matters as the Board desires, with the exception of the establishment of policy or the review and approval of major matters. Members are elected to the Executive Committee for a two-year term.

The National Science Foundation was created by Congress early in 1950. The Director and staff of the National Science Foundation have initiated programs in support of basic research in the medical, mathematical, physical, engineering, and biological sciences. Applications are also being received for National Science Foundation graduate fellowships for the academic year 1952-1953 in the same fields. The Foundation expects to award about 400 such fellowships. Applications may be received from the Fellowship Office, National Research Council, Washington 25, D. C.

Tentative Guide for Use of Prospective Grantees in Preparing Scientific Research Proposals.—The first draft of a guide to assist scientific research investigators in the preparation of proposals for National Science Foundation research grants has been issued by the Foundation. Copies of the guide will be distributed widely to universities and colleges, laboratories, and other organizations in a position to carry on competent scientific research.

The Foundation will support basic research in the mathematical, physical, medical, biological, and engineering sciences by making grants for such research to educational, industrial, governmental, or other institutions, or individuals. Ordinarily grants will be awarded to institutions for research by specified persons.

In reviewing proposals, the Foundation will emphasize the scientific merit of the suggested research, including the competence of the scientist under whom the study will be made.

During the current fiscal year the Foundation has earmarked approximately $1,500,000 for support of basic scientific research.

Laboratory Training Courses.—The Public Health Service, Federal Security Agency, has announced a schedule of laboratory training courses to be given by the Communicable Disease Center, Chamblee, Ga., during 1952. Included will be courses in the laboratory diagnosis of bacterial diseases, of parasitic diseases, of virus diseases, of rabies, and of tuberculosis, and

courses on identification of medically important arthropods, on virus isolation and identification techniques, on special problems in enteric bacteriology, and on phage typing of Salmonella typhi. Information and application forms should be requested from the Chief, Laboratory Training Services, Communicable Disease Center, United States Public Health Service, P. O. Box 185, Chamblee, Ga.

Congress on Diabetes Mellitus.—A congress on diabetes mellitus will be held at Leyden, Netherlands, from July 7 to 12, 1952, organized by the International Diabetes Federation. For further details, persons interested are kindly requested to apply to Dr. F. Gerritzen, 33, Prinsegracht, The Hague, Netherlands.

Book Reviews

The Human Colon: An Experimental Study Based on Direct Observation of Four Fistulous Subjects. By William J. Grace, M.D.; Stewart Wolf, M.D., and Harold G. Wolff, M.D. Price, $7.50. Pp. 239, with 112 illustrations, 31 in full color. Paul B. Hoeber, Inc. (Medical Book Department of Harper & Brothers), 49 E. 33d St., New York 16, 1951.

In this monograph, the authors have investigated and described the reaction of portions of exposed colons in four fistulous subjects. They observed the response of the colon directly by pharmacological and physical agents, and also the reaction of the colon when the patients were stimulated during anger and fear and during satisfaction and pain.

In their study they noted color changes in the mucosa of the colon, changes in secretory response and motor activity, and changes on kymographic tracings.

They are of the opinion that in all four fistulous subjects they were able to demonstrate that situations productive of conflict, resentment, and hostility were associated with hypermotility and hypersecretion of the enzyme lysozyme and of mucus. Dejection and fear, however, were associated with hypofunction of most of the large intestine. Pallor and relaxation were observed, as well as diminished contractile activity and low concentration of lysozyme in colonic secretions. In two patients who sustained hyperfunction during anger and resentment, the appearance of petechial hemorrhages was noted.

The authors devote a chapter to ulcerative colitis. They studied the personality features and reactions of 19 patients. Ulcerative colitis they view as a stress disorder. They explored the emotional response, the patients' background, and their family relationships and are of the opinion that the onset and exacerbations of ulcerative colitis correspond closely to life experiences which the patients interpreted as threatening.

In summary, these authors are of the opinion that the colon of man participates in the reaction patterns to threatening events in the patients' life situations and that changes involving colonic hyperfunction, at first altogether functional and transitory, may, when unduly sustained, result in structural damage and disease.

This monograph is well written and well illustrated and should be of interest in correlating the close relationship of colonic response to emotional stress.

The Physiology of the Newborn Infant. Second edition. By Clement A. Smith, M.D. Price, $7.50. Pp. 348, with 52 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

Smith's recently revised book deals with both the fundamental and the practical aspects of physiology in the newly born infant. The significance of the subject matter to the practice of pediatrics cannot be overestimated. A thorough understanding of fetal physiology and the alterations that occur at the time of birth is essential for ideal management of clinical problems encountered by the physician during the critical first days of the baby's life.

The general subjects of respiration, circulation, the blood, digestion, body heat regulation, and all phases of metabolism in the newborn are discussed in separate chapters in a highly authoritative manner. Because of the special importance of the water and electrolyte exchanges during this period of life, the peculiarities of renal function in the infant are given careful consideration. With the renewed interest in congenital heart disorders, the chapter on circulation is particularly welcome.

A final chapter on neonatal endocrinology is appropriately included in the monograph. In addition to supplying up-to-date information on the general status of the endocrine glands during the first weeks of life, the author directs special attention to certain questions most frequently

arising in the mind of the physician, such as those concerning the normality of breast and sex organ development, the abnormalities of infants of certain diabetic or prediabetic mothers, and the place, if any, of endocrine substances in the general management of newborn or premature infants. In the reviewer's opinion this book should be in the library of every physician who is called upon to deal with problems of the newborn.

Management of Celiac Disease. By Sidney V. Haas, M.D., and Merrill P. Haas, M.D. Price, $5. Pp. 188, with 12 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1951.

This timely monograph by Dr. Sidney V. Haas, who introduced banana feeding in the therapy of celiac disease, and his son represents the most extensive report published thus far on the subject. The first two-thirds of the book deal with the historical aspects of the problem, the various theories of etiology, and the methods of treatment proposed by different workers in the field. The remaining pages are devoted to the authors' own experience and opinions.

On the whole, the subject is treated comprehensively and objectively. The writers' style is clear and direct, and their approach to controversial aspects of the problems of celiac disease is fair and judicious. An attempt is made to compare therapeutic results and prognosis on the basis of differences in dietary management. Although the authors do not claim to know the underlying cause of celiac disease, their conviction is strong that its main manifestations are related to the use of polysaccharides (complex carbohydrates) in the diet in susceptible infants. According to their view, fats are tolerated well, so long as these complex polysaccharides are completely excluded from the diet. Monosaccharides or simple sugars, as well as proteins, are tolerated satisfactorily. "Fat intolerance" manifests itself only when the offending complex carbohydrates—starch, lactose, sucrose, etc.—are included in the diet. When the diet is high in proteins and moderate in fat and contains carbohydrate exclusively in the form of simple sugars (as in ripe banana and other fruits and certain vegetables), recovery occurs eventually in nearly all cases of celiac disease, according to the authors' conclusions.

Current Therapy, 1951: Latest Approved Methods of Treatment for the Practicing Physician. Edited by Howard F. Conn. Price, $10. Pp. 699. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

Here is a book that should be immensely popular with practicing physicians. Therapy for all the diseases commonly encountered in medical practice is outlined in enough detail to be entirely practicable for the busy practitioner. A group of 12 associate editors, all authorities in their various fields, has supervised the accumulation of material by a total of 275 authors—each of whom presents his own ideas of treatment of the various conditions. In some instances two or three authors give their version of therapy for a given disease. While many of the writers have made significant original contributions to the knowledge of the conditions about which they write, the plan is to have them present the consensus of well-qualified opinion on the treatment of the disease assigned to them. Practically all the contributors are members of medical school faculties, well known to readers of current medical literature. Their plans of treatment will be read with interest and profit by the physicians who read this volume.

The Quantitation of Mixtures of Hemoglobin Derivatives by Photoelectric Spectrophotometry. By Francis T. Hunter, M.D. Price, $8.50. Pp. 248, with 55 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

Hunter's monograph gives "the principles underlying the quantitation of pigment mixtures in general, and the mixture of certain hemoglobin derivatives in particular. . . ." The first 50 pages of the book are devoted to the theory of and the mathematical computations involved in the spectrophotometric analysis of two- and three-component systems. There are instructions for the preparation of conversion charts and nomograms. In the second 50 pages there are procedures for the spectrophotometric determination of such hemoglobin pigments as oxyhemoglobin, carbon monoxide hemoglobin, and neutral hemoglobin. Spectrophotometric methods for the determination of oxygen saturation and erythrocyte volume are also given. Unfortunately, no data are presented to show the reliability or advantages of these techniques when compared

with the procedures currently being used in many clinical laboratories. The last section of the book presents the charts and nomograms secured by the author for the hemoglobin derivatives mentioned in the text.

For those laboratories where large numbers of determinations are made for different hemoglobin derivatives, this book may aid in establishing procedures which in the long run will save time.

Principles and Practice of Obstetrics. By Joseph Bolivar DeLee. Tenth edition. Edited by J. P. Greenhill, M.D. Price, $12. Pp. 1020, with 1140 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

When a medical textbook grows to be nearly 50 years old and has required new editions to supply its readers with up-to-date copies every few years, it can safely be called a success. Such is the record of this book written originally by Dr. DeLee, then edited and improved by him in conjunction with Dr. Greenhill, and finally, in its present form, prepared by Dr. Greenhill alone.

The tenth edition—the 1951 model, so to speak—is not unlike a new car which is modern in every way, streamlined and bearing little resemblance to its 1910 progenitor. It is needless to add, speaking of the book, that medical students, medical teachers, and practitioners will continue to like it and will learn much from it. Indeed, it can be warmly recommended to anyone.

Perhaps the most important reason for its popularity is the fact that each edition has been assembled for students and practitioners; their needs have been constantly held in view in every printing. Dr. DeLee wrote in a copy of the first edition which he gave to a young friend who at the time had just completed his first year in medical school, "May this volume be of interest and profit." Teachers who make textbooks for their pupils with such a goal in mind are likely to achieve far-reaching results.

The Effect of Hormones upon the Testis and Accessory Sex Organs. By Norris J. Heckel, M.D. Price, $2.25. Pp. 73, with 23 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

As with the other monographs of the American Lecture Series, Dr. Heckel tries to present a complex subject in a concise but abbreviated form. This type of presentation has many shortcomings in a field where so much controversy exists in regard to diagnosis, treatment, and even basic gonadal physiology. It has not been firmly established, for instance, that orchiopexy or even gonadotropin treatment of cryptorchism is a clinically justified procedure as Dr. Heckel would advocate. Again, one might take issue with the statement that "testosterone is produced by the Leydig cells." The physiological Leydig-cell androgen has not been established. In general, however, this short monograph is well presented and written and should be useful to the general practitioner.

Better Nursing: A Study of Nursing Care and Education in Washington. By Jean A. Curran and Helen L. Bunge. Price, $3. Pp. 174. University of Washington Press, 111 Thomson Hall, Seattle 5, 1951.

Although this is a study of nursing service and nursing education in Washington state, the problems and deficiencies revealed are not limited to any locality. The study has nation-wide significance and applicability and contains information of importance to doctors, nurses, educators, hospital administrators and their staffs, and finally to the public, which is and will be the most vitally affected if the problems involved in nursing are not solved. The co-authors of the report acted as directors of the study and as consultants to the Washington Advisory Committee on Nursing Service and Training Programs and are well-known authorities in their fields.

The Committee drew for its information upon extensive amounts of reference material and the findings of current and previous studies made in Washington and elsewhere. Visits were made for purposes of observation and comparison to selected hospitals and schools of professional and practical nursing. Experts were consulted, and conferences were held with groups and

leaders in nursing and related fields. As a result of these investigations, the following problems were identified and analyzed: (1) the quantitative shortages in all categories of personnel, as well as qualitative shortcomings in nursing service; (2) the unsatisfactory interpersonal relationships among members of the health groups because of mutual misunderstanding and lack of cooperation, (3) the inadequate and improper financial support for nursing education, (4) the impersonalized service on the part of members of hospital staffs, (5) the failure to define and limit the functions of various levels of nursing and to utilize effectively the present types and potential sources of nurse power, (6) the need of flexibility in state regulation of nursing education to permit experimentation with and development of nontraditional nursing education programs, and (7) the increasing demands upon the present inadequate supply of nurses to meet military needs.

The report contains summaries and conclusions upon which are based the twenty-two constructive recommendations that seem possible of implementation and can well serve as a model for studies of nursing in other states.

Diseases in Old Age: A Clinical and Pathological Study of 7,941 Individuals over 61 Years of Age. By Robert T. Monroe, M.D. Price, $5. Pp. 407. Harvard University Press, Jewitt House, 44 Francis Ave., Cambridge 38, Mass., 1951.

Monroe's monograph is based upon a study of the records of 7,941 persons past the age of 61 years who entered the Peter Bent Brigham Hospital, Boston, from its opening in March, 1913, to March 1943. The inclusion of the early data with those gathered more recently obviously makes the study of rather limited value, since medicine has changed considerably during the past 15 years. For example, consider the value of the data on lobar (pneumococcic) pneumonia before the advent of antibiotic agents in light of medicine today. The same is true for the psychoses, psychoneuroses, coronary artery disease, and diagnostic laboratory procedures, including liver-function tests, electrocardiography, and immunologic, vitamin, and hematologic studies, to mention only a few. Furthermore, many diseases were unknown during the early period of this study.

Most of the study is of a statistical nature. The data were obtained from the records and not by the author. They represent the past medical experience with old persons of others working during a period of the most rapid progress in medical history. It is the opinion of the reviewer that this type of monograph can serve little purpose to medicine. It is hoped that some important use may be found for all the detailed data, though it is difficult to imagine any real contribution made by these analyses. The book may interest a few persons who would like to look back a bit to review the experience with old people at a good American hospital. But it must be remembered that many of these experiences can today serve historically only, and any attempt to apply many of the data in present-day clinical management of patients can lead only to error. Furthermore, it should also be remembered that many of the data, though obtained in old persons, are not necessarily peculiar to old persons.

Text-Book of Medicine. First Edition. Edited by E. Noble Chamberlain. Price, $10. Pp. 962, with 266 illustrations. Williams & Wilkins Company, Mt. Royal & Guilford Aves., Baltimore 2, 1951.

The authors of this book sustain the perfectly reasonable thesis that if the present trend is continued the teaching and practice of medicine may be reduced to absurdity by encrusting them in a mass of more or less unnecessary and complicated laboratory work which beclouds rather than clarifies the issue. It takes British common sense and conservatism, however, to do more than merely fuss about this and actually to publish a textbook of medicine reduced to simple terms and pretty well stripped of superfluous verbiage. The result is interesting and surprisingly useful; one wonders whether students will not get a really excellent idea of the natural history of disease from discussions of this sort. It must be admitted, however, that the British, not as flush with lavish mechanical equipment as we are, may be making a virtue of necessity; nonetheless American textbook writers can learn something here, including use of the language with clearness, force, and precision.

Amenorrhea. By Lawrence M. Randall, M.D., and Thomas W. McElin, M.D. Price, $2.25. Pp. 81. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1951.

This small volume "Amenorrhea" consists chiefly of a compilation of one-paragraph abstracts of publications on the subject. To the student who is hoping to find a critical evaluation of the present state of knowledge on amenorrhea, this monograph is very disappointing. It certainly does not measure up to the high standard previously set for publications of the American Lecture Series. There is a short chapter entitled "War Amenorrhea," an unfortunate designation for a functional clinical state that may also occur in peace time. There is another brief chapter entitled "Russian Investigation." More than half of the book is devoted to treatment, which is, admittedly, a difficult subject to present, and one may well sympathize with the authors.

Werdnig-Hoffmann's Infantile Progressive Muscular Atrophy. By Sven Brandt. Price, 20 kroner. Pp. 328, with photographs and tables. Ejnar Munksgaards Forlag, Nøregade 6, København, K, Denmark, 1950.

This impressive work by Sven Brandt deals with the clinical aspects, the pathology, and the heredity of infantile progressive muscular atrophy and its relation to Oppenheim's amyotonia congenita and other morbid conditions with laxity of joints or muscles in infants. The author's study is based on a series of 156 cases, 131 so-called primary and 25 secondary cases, and represents all the material on this disease that Brandt was able to accumulate in Denmark. The author gives an exhaustive survey of publications on "myatonia congenita," infantile progressive spinal muscular atrophy, and congenital or very early cases of muscular dystrophy. He discusses the attempts to differentiate from a pathological and clinical viewpoint between Oppenheim's amyotonia and Werdnig-Hoffmann disease. The clinical syndrome of infantile progressive muscular atrophy, its course and prognosis, the anatomy, etiology, and pathogenesis, the treatment, prophylaxis, and eugenic measures are thoroughly discussed and the pedigrees and case histories reported. A final chapter deals with the differential diagnosis.

The author arrives at the following conclusion: Neither the cases of the literature nor the cases studied in this work "confirm the existence of any well-characterized disease corresponding to the 'amyotonia congenita' described by Oppenheim in 1900." He found that on closer examination these cases have been found to be manifestations of infantile progressive muscular atrophy. Many morbid conditions in childhood are accompanied with muscular flabbiness, and the diagnosis of amyotonia congenita may be used only to designate cases in which a specific causation remains unknown. Cases which show improvement, and, for this reason, are not to be confused with progressive muscular atrophy, are very rare. The progressive muscular atrophy may be spinal or myogenic, a point which can be ascertained only by means of particular methods of examination. Heredity proved to "play a dominant role as an etiological factor," and a hereditary metabolic defect, expressed in disturbances in the utilization of vitamin E or other vitamins, must be considered. Vitamin treatment per se usually fails. Symptomatic muscular flabbiness is seen, e. g., in the presence of rachitic symptoms, in chronic dyspepsia, in cases of cortical atrophy and central nervous system syphilis, and in toxoplasmosis; observation of the child over a longer period often leads to the right diagnosis.

The Central Nervous System During Insulin Shock, with Special Reference to Structural Activity Changes of the Nerve Cells: An Experimental Histological Study. *Acta psychiatrica et neurologica,* Supplement 64. Translated from the Danish by A. Rousing. By Knud Aage Lorentzen. No price given. Pp. 83, with 37 illustrations. Ejnar Munksgaards, Forlag, Nørregade 6, København, K., Denmark, 1950.

The author presents a monographic study of the histological changes of the central nervous system in rabbits treated with insulin shock. Particular attention was given to the study of nerve cells in which, in the author's opinion, structural activity changes can be demonstrated very exactly by Einarson's "gallocyanin-chromalum staining" method. The author gives a good review of the literature of earlier experimental studies and casuistic publications. He then proceeds to discuss his personal investigations on rabbits, describing the clinical picture characterized by a coma, lasting for one or more hours during which two to six attacks of tonic-clonic convulsions

developed. Einarson's method for the staining of the chromatin substances is, according to the author, far superior to the Nissl stain, which he declares is "absolutely unfit for sections from the central nervous system in which the Nissl picture is to be used in the evaluation of the activity changes of the nerve cells, and also to some extent of the usual degenerative changes." He calls Einarson's method "to a great extent independent of the pH of the dye solution, for which reason all differentiation can be omitted." He also points to Einarson's statement that "the aniline dyes stain various degeneration products of the cytoplasm of the nerve cells with great intensity, so that the cytoplasm appears to be 'rich' in Nissl substance" which then leads to misinterpretations. He describes the "histologic picture of the chromatin substance, as it appears in the various stages of activity as illustrated by the gallocyanin-cromalum [*sic*] staining method." A number of other staining methods were also used, without giving additional information. Rabbit brains, so-called acute brains obtained from animals which died in the first shock and "chronic" brains from animals which had been given daily insulin shocks for 6 to 28 days were examined. It was found that "repeated insulin shock treatment will induce an increasing chromophoby [*sic*] of the nerve cells in experimental animals. . . . After the cessation of the treatment the resynthesized nucleoprotein (the chromatin) will again accumulate in the cells which have not been exposed to irreparable atrophy." In the cerebral cortex a diffuse "dropping out" of cells was found, showing that "the vulnerability of the nerve cells during insulin shock treatment will invariably result in the destruction of some of its nerve cells." No clinical changes accompanied the histological damage. Glia changes were regarded as equivocal, although they again were mostly found in the cerebral cortex and consisted predominantly of a slight increase in the oligodendroglia and astroglia. It is unfortunate that the numerous photographs illustrating the text are not good enough to permit the reader to evaluate the findings.

Psychosomatic Gynecology: Including Problems of Obstetrical Care. By William S. Kroger, M.D., and S. Charles Freed, M.D. Price, $8. Pp. 503. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1951.

This comprehensive volume really deals with the psychiatric problems originating in or bound up with gynecological disturbances. It represents intensive study, is well documented, and covers a wide range of subject matter. Beginning with the psychiatry of the maternal-fetal relationship, one is carried on through adolescence, the disturbances of menstruation, pregnancy, etc. There is a good deal of the usual esoteric jargon of the professional psychiatrist, which the reviewer finds at times difficult to follow. However, there is much that makes sense in this excellent volume which should undoubtedly be on the desk of every gynecologist and obstetrician, as well as general physician.

Clinical Unipolar Electrocardiography. By B. S. Lipman, M.D., and E. Massie, M.D. First edition. Price, $5. Pp. 232, with 191 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1951.

As indicated by the title, the authors have limited their discussion solely to unipolar leads. Although the literature is already replete with texts and articles dealing with the subject, this brief monograph is singularly successful in presenting the material in easily readable and understandable form.

The first two chapters deal with the technique of unipolar electrocardiography and with the physiological principles underlying the normal electrocardiographic patterns. After this introduction, an explanation of the various electrical positions of the heart is given while the remaining chapters deal with the commoner electrocardiographic abnormalities. These include ventricular enlargement, bundle branch block, myocardial infarction, and the various patterns seen with ventricular aneurysm, pericarditis, quinidine effect, hypopotassemia, etc.

Although intended primarily for the beginner, the book will serve as an excellent refresher for the busy internist. It is not, however, a detailed treatise, and those desiring a more comprehensive discussion of the topic will necessarily have to refer to more detailed texts.

The book is generously illustrated throughout with diagrams, and the last 63 pages contain 89 photographs of electrocardiograms illustrating various topics discussed in the text. A bibliography containing 219 references is included.

Conference on Factors Regulating Blood Pressure: Transactions of the Fourth Conference. Edited by Benjamin W. Zweifach and Ephraim Shorr. Price, $3. Pp. 219, with 39 illustrations. Josiah Macy, Jr., Foundation, 565 Park Ave., New York 21, 1951.

The transactions of the fourth Macy Conference on Factors Regulating Blood Pressure, held on Feb. 23 and 24, 1950, are presented in this publication. The conference was attended by prominent investigators in the field. The subjects discussed include anatomic considerations of hypertension, classification of hypertension, renal adjustments related to hypertension, endocrine factors related to hypertension, VEM and VDM (basoexcitor and vasodepressor material), renin, and pressor substances. These transactions are always interesting and are of considerable value not only to those engaged in studying blood vessel function but also to clinicians.

Electron Microscopic Histology of the Heart: An Application of Electron-Microscopic Research to Physiology. By Bruno Kisch, M.D., in collaboration with Joan M. Bardet. Price, $5. Pp. 106, with illustrations. Brooklyn Medical Press, P. O. Box 99, Cathedral Station, New York 25, 1951.

This work consists of 62 pages of electron micrographs of fair quality and 44 pages of text. The material examined consisted of thin sections of heart muscles from C_3H and Webster strain mice. The photographs are claimed to prove that blood capillaries enter into the individual muscle fibers of the heart and that a higher concentration of sarcosomes is found between the myofibrils of the heart than in striated muscle. Numerous comments are made on the Z bands, sarcolemma, and fiber structures. A diagram of a heart muscle summarizes the histologic findings.

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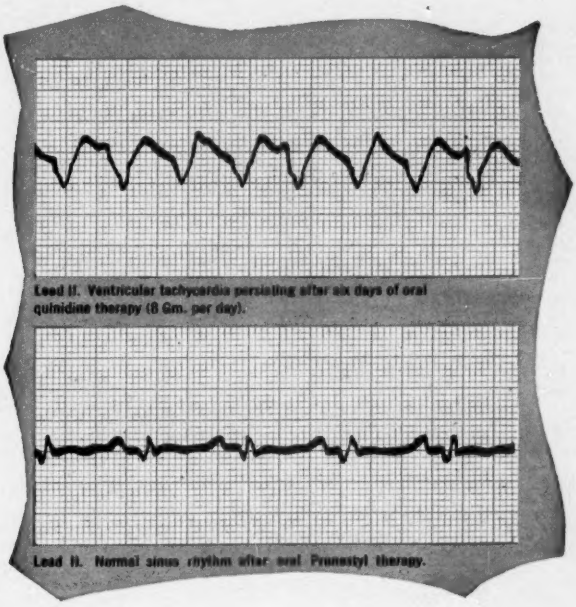

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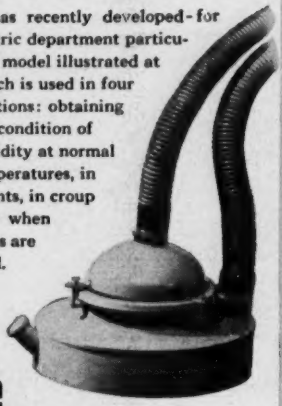

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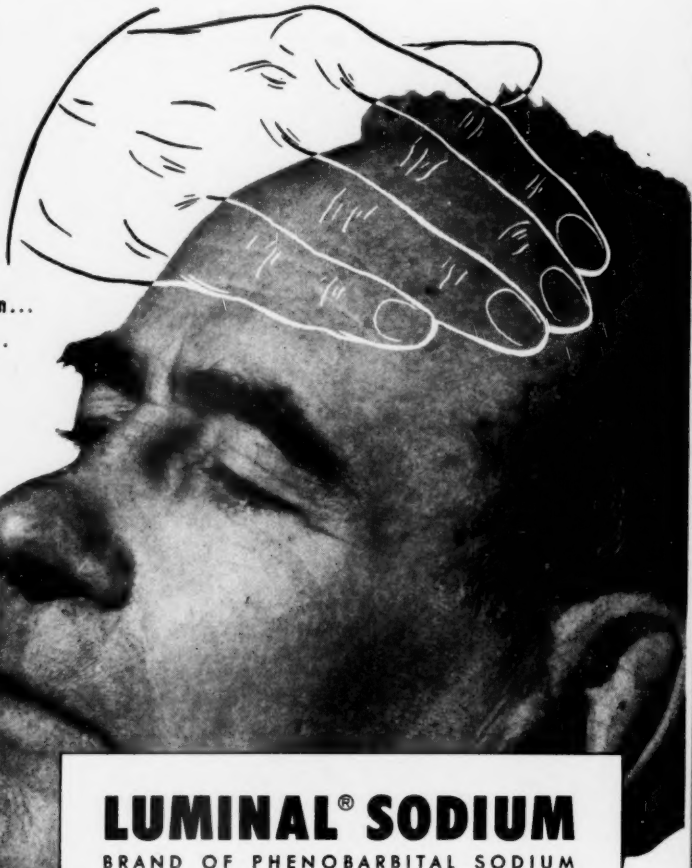

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